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REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim 4 has been amended to include a pharmacologically acceptable carrier. Support is found at page 9, line 4.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, is deemed to be overcome in view of this amendment.

A terminal disclaimer is submitted with regard to U.S. patent number 6,608,092.

The rejection of claims 1, 2 and 4 under the judicially created doctrine of obviousness-type double patenting is thus deemed to be overcome.

A second terminal disclaimer is submitted with respect to U.S. patent number 6,462,058.

The rejection of claims 1, 2 and 4 under the judicially created doctrine of obviousness-type double patenting is thus deemed to be overcome.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102 as being anticipated by Barberich et al. (2001/0025107), Nohara et al. (U.S. 4,628,098) and Kato et al. (U.S. 6,002,011). This ground of rejection is respectfully traversed.

1. Subject matter of the present invention

The subject matter of the present invention is not (-)-lansoprazole ((S)-lansoprazole) itself, but the crystal of (-) lansoprazole, that is, crystalline (S)-lansoprazole and a pharmaceutical composition containing the same.

2. Disclosure of the cited Documents

U.S. 4,628,098

Although U.S. 4,628,098 discloses the crystal of racemic lansoprazole etc. and the use thereof, the crystal of optically active (S)-lansoprazole is not specifically described in the reference.

U.S. 6,002,011

U.S. 6,002,011 discloses the crystal of racemic lansoprazole which does not substantially contain solvent (Example 1). However, the crystal of (S)-lansoprazole is not specifically described in the reference.

U.S. 2001/0025107

U.S. 2001/0025107 discloses a pharmaceutical composition containing (S)-lansoprazole and treating method for ulcer etc. using (S)-lansoprazole. However, there is no description or suggestion about crystalline (S)-lansoprazole in the reference.

3. Novelty over cited references

As described above, none of the cited references disclose the subject matter of the present invention: crystal of (-)-lansoprazole, that is, crystalline (S)-lansoprazole. Therefore, the present invention is novel over the cited references.

In view of the foregoing, reconsideration and withdrawal of this ground of rejection is respectfully solicited.

Claims 1, 2 and 4 are further rejected under 35 U.S.C. 103 as being unpatentable over the combined teachings of Barberich et al., Nohara et al., and Kato et al. in view of Chemical and Engineering News, U.S. Pharmacopia and Concise Encyclopedia of Chemistry. This ground of rejection is respectfully traversed.

4. Non-obviousness of the present invention

(1) It should be noted that the racemic lansoprazole and the optically active lansoprazole have quite different properties. In particular, their stability and solubility are quite different from each other. Since these properties have a great influence on crystallization, such difference clearly shows that (S)-lansoprazole cannot be crystallized by the same manner as crystallization of racemic lansoprazole. Further, since the characteristic peaks at interplanar spacings of the X-ray powder diffraction of both compounds are different from each other as shown in attached Appendix I, crystalline forms of both compounds are also different from each other. It can therefore be said that, as a chemical compound, (S)-lansoprazole is completely different from racemic lansoprazole.

For studying crystallization of optically active lansoprazole, a person skilled in the art would refer to known Reference Document 2 (WO07/02261) which discloses the purification of optically active isomer of benzimidazole compound such as lansoprazole or Reference Document 3 (WO96/02535) which discloses the production of optically active lansoprazole etc. by asymmetric oxidation, rather than cited reference U.S. 4,628,098 and U.S. 6,002,011 which discloses crystallization of racemic lansoprazole.

(2) Further, whether or not a compound can be crystallized cannot be presumed. A person skilled in the art knows this very well.

For example, the New Scientists Group, page 6, lines 8-11 (attached Reference Document 1) discloses as follows.

"As seen from the above example of glycerin, in case of a newly found or synthesized chemical compound, in may cases, one often has a very hard time until a first crystal is obtained. That is, even if a solution of a compound is cooled, it is not easily solidified. However, once any one has succeeded in crystallization at any place in the world, since then, the crystallization can be readily carried out. As the number of crystallization increases, crystallization can be carried out more easily."

(3) Indeed, Reference Document 3 (WO96/02535) and Reference Document 2 (WO97/02261) disclose (S)-lansoprazole. However, in these documents, (S)-lansoprazole is obtained in the form of an oil. No crystals of (S)-lansoprazole are obtained in these documents. This shows that (S)-lansoprazole in the form of crystals is very difficult to obtain (see Example 11 of Reference Document 2 and Example 21 of Reference Document 3).

The applicant of Reference Documents 2 and 3, i.e., ASTRA AKTEBOLAG, has studied the production and purification methods of benzimidazole proton pump inhibitor (PPI) compounds including lansoprazole for a long term. In spite of such studies, as to optically active lansoprazole, only the compound in the form of an oil has been obtained as shown by Reference Documents 2 and 3. Then, from Reference Documents 2 and 3, a person skilled in the art would presume that optically active (S)-lansoprazole in the form of crystals cannot be obtained.

In fact, as seen from Example 11 of Reference Document 2, **in case of lansoprazole, racemic lansoprazole precipitates as crystals more easily in comparison with the optically active isomer and the mother liquor has a higher optical purity.** This suggests that, even if racemic lansoprazole can be crystallized, its optically active isomer can be hardly crystallized.

Further, in Reference Document 2, the purification requires precipitation of the crystals of the racemic compound, concentration of the remaining mother liquor to improve the optical purity of the mother liquor and then repetition of these procedures. Even if these procedures are repeated, crystals of the optically active isomer cannot be obtained and the isomer is obtained as an oil.

That is, Reference Documents 2 and 3 show that, in case of lansoprazole, (i) racemic lansoprazole precipitates as crystals more easily in comparison with the optically active isomer and the mother liquor has a higher optical purity, and (ii) crystals of the optically active isomer cannot be obtained even if concentration of the mother liquid is repeated. This certainly suggests the difficulty of the crystallization of (S)-lansoprazole.

Thus, even if the presence of asymmetric center in lansoprazole and method of resolution of an optically active isomer, and also the presence of crystal or racemic compound in the cited references, U.S. 4,628,098, U.S. 6,002,0121 and the like have been known, such prior art knowledge does not facilitate crystallization of an optically active isomer. In other words, **the prior art including Reference Documents 2 and 3 suggests that the crystallization of the optically active isomer of lansoprazole would be very difficult, while racemic lansoprazole can be crystallized. This would dissuade a person skilled in the art from trying the crystallization of the optically active isomer of lansoprazole, rather than to motivate one skilled in the art towards the present invention.**

(4) Moreover, the optical purity of (S)-lansoprazole is improved by crystallization according to the present invention. As seen from Example 2 and Reference Example 2 of the present specification, the optical purity of amorphous (S)-lansoprazole is 93.3% ee, while the optical purity of the crystal of (S)-lansoprazole is improved up to 99.43% ee.

In contrast, as mentioned for Example 11 of Reference Document 2, the above Reference Document 2 teach that, in case of optically active (S)-isomer of lansoprazole, a crystal having high optical purity can hardly obtained. Nevertheless, according to the present invention, the crystal having the high optical purity of lansoprazole is unexpectedly obtained. Thus, as described in the present specification, there can be provided the crystal whose handling is facilitated and which is suitable for industrial production and applicable for medicines.

(5) Also, the Examiner rejects the patentability of the present invention as being obvious by citing (i) Chemical & Engineering News, (ii) U.S. Pharmacopia, (iii) Concise Encyclopedia Chemistry, as well as above-mentioned cited references. However, in the cited references (ii) and (iii), it is merely described generally that a crystal may exist in various forms and each one of the crystal forms has the characteristic lattice pattern in the X-ray powder diffraction. Therefore, these cited references are of no help at all to solve the problem of the present invention that is to obtain

a crystal of optically active isomer of particular compound; lansoprazole. In addition, the description of the cited reference (i) is also generic. But since it was issued on February, 2003, its citation is respectfully submitted to be improper.

(6) As mentioned above, the production of the crystal of (S)-lansoprazole of the present invention is not obvious to a person skilled in the art in view of the cited references, and the crystallization can be hardly carried out easily. Moreover, the obtained crystal of the present invention has high optical purity and is stable. Thus, the present invention makes the industrial implementation as a medicine possible.

In view of the above, the present invention is unobvious for a person in the art, and therefore patentable over the cited references.

In view of the foregoing, reconsideration and withdrawal of this ground of rejection is respectfully solicited.

Lastly, claims 1, 2 and 4 are rejected under the judicially created doctrine of obviousness-type double patenting with respect to claims 1-8 and 10 of U.S. Patent No. 4,628,098. This ground of rejection is respectfully traversed.

As mentioned above, since the '098 patent is directed to a compound such as racemic lansoprazole while the present invention is directed to a crystal of optically active (S)-lansoprazole, the present invention is unobvious over U.S. Patent No. 4,628,098.

Reconsideration and withdrawal of this ground of rejection is respectfully solicited.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

Akira FUJISHIMA et al.

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Appendix I

Comparison of Properties of Racemic and (S)-Lansoprazole

	Racemic Lansoprazole	(S)-Lansoprazole
X-ray powder diffraction, peaks at interplanar spacings (Å)	15.22, 15.06, 6.18, 6.15, 5.20, 5.02, 4.72, 3.96, 3.85, 3.76, 3.55, 3.46, 3.19, 3.11, 2.93, 2.90, 2.85, 2.69, 2.66	11.68, 6.78, 5.84, 5.73, 4.43, 4.09, 3.94, 3.90, 3.69, 3.41, 3.11

Reference Document 1

新科学

ニューサイエンス・オデッセイ

沢サイエンス・オデッセイ編

Post Psychology
Post Physics
New System Theory

THE NEW SCIENTISTS

RUPERT SHELDRAKE
The Hypothesis of Formative Causation

by Hanazumi Yôko

ルパート・シェルドレイク
一九八一年、イギリスのケンブリッジ大学で教職をとっていた若き生化学者シェルドレイクは、生物の形態形成に関する自らの長年の疑問に答えるべく大胆な仮説を発表した。"A New Science of Life"（邦訳『生命のニューサイエンス』工作舎）は発表後たちまち世界の科学界に賛否両論嵐の議論を巻き起こした。イギリスの科学誌『ニューサイエンティスト』とアメリカのターリータウン財団が仮説を検証する実験方法を公募し、今後の展開が注目される。

1　ルパート・シェルドレイクの形態形成場理論
――ウサギはなぜウサギにしかなれないのか

●グリセリンをつなぐ"見えない場"

今から一五〇年ほど前、天然脂肪から無色の液体グリセリンが抽出された。グリセリンは甘味料や医薬、ニトログリセリンの原料として広く用いられるようになった。だがこの液体にはひとつ、不可解な性質があった。化学者たちはグリセリンの結晶を得ようとして急冷却や再加熱などあらゆる方法を試みたが、この液体はなぜかいっこうに結晶しようとしなかったのである。そしてついには、理由は不明だが、固体グリセリンはないものと思われるまでになった。

ところが、今世紀初めになっておかしなことが起こった。オーストリアのウィーンの工場からロンドンの得意先にグリセリンが貨物船で送られることになり、途中、船は大きな嵐に見舞われたが無事ロンドンに到着した。そして注文主が中を調べるためグリセリンの樽をあけてみると、そのうちの一樽が見事に結晶化していたのだ。「こんな状態では使いものにならない」と注文主は困惑したが、喜

んだのは化学者たちである。彼らは先を争ってこの世界初のグリセリン結晶を手に入れ、自前の液体グリセリンに種子づけして結晶づくりにはげんだ。それまで二〇〇年近く手こずらされていたことがウソのようにグリセリンは世界中で次々と結晶化していった。そしてアメリカのある研究所で同じ結晶を手に入れ試料の結晶化に成功したとき、驚くべきことが起こった。研究室内にあったすべてのグリセリンが勝手に結晶化しはじめたのだ。なかには密封容器に入っていたものさえあった！　それはあたかも試料のグリセリンが結晶化するプロセスを周囲のグリセリンが〝学習〟し、いっせいに模倣したかのようだった……。

このグリセリンの例のように、新しく発見されたり合成されたりした化学物質の場合、最初の結晶を得るのに非常に手こずらされることがよくある。つまり液体状態の物質を冷やしてもおいそれと固まってくれないのだ。ところがひとたび世界のどこかで結晶化に成功すると、その後は容易に結晶化するようになり、結晶した回数がふえればふえるほど結晶化は容易さを増す――この〝現象〟は従来、結晶の断片が溶液に「感染」するためと考えられてきた。「感染」は人間を媒介にして起こることもあれば、種子が大気中を運ばれて溶液の上に落ちる空気感染もある。アメリカの研究所で種子づけしていないグリセリンが突然結晶化したのもそう考えれば説明がつく。だが、その後世界中の研究所で種子づけしないでもグリセリンを結晶させられるようになったことについてはどうか。これも、研究所と研究所を行き来する化学者たちの毛髪や衣服に結晶小片が付着して運ばれたとか、〝空気感染〟がもっと大規模に起こったとか、その程度の理由で本当に説明しきれるものなのだろうか。現実

的に考えても世界中の研究所を飛びまわって〝種子を配達する〟化学者がそうたくさんいるとは思えないし、まして小さな結晶小片が風にのって太平洋や大西洋を横断して無数の建物の中の特定の建物の一室――グリセリン試料のある研究所の一室――に入りこみ、試料の上にうまく着地する確率などといったらごくごくわずかなはずである。仮にそうした可能性を認めたとしても、このグリセリンのケースについては解決されない問題が残る。それは、室内の空気と隔離されていた密封容器の中でもグリセリンが結晶した事実である。

さて、この結晶にはもうひとつ興味深い点がある。それは、まだ一度も結晶したことのない化学物質がいったいどのような結晶形態をとるか、前もって予測することが不可能とはいわないまでもきわめて困難なことである。その化学組成から化学的、物理的、そして経験的に結晶形態を予測できるはずだと思われるかもしれない。確かにそれは可能だが、理論的に描き出せる結晶の青写真は数十種類、いや数百種類にものぼり、確率はどれも同じくらい低くてそのどれになるかを前もって決定することはできない（少なくとも現在の科学では不可能だ）。そして実際に結晶ができてはじめてどれが正しかったかがわかる。しかも物質がひとたびその結晶形態を「選ぶ」と、それ以後はずっとその形態をとり続ける。だが今日の科学はなぜ特定の形態が選ばれたのかという最初の問いに答えられないのと同じ理由で、どうして初めの形態に定着するのかという疑問にも答えることができないでいる。

化学の現場で起こっているこの結晶をめぐる不思議な現象について二十世紀の現代科学がいまだに明確な答えを出していないことに、意外な感じを覚える人も多いだろう。宇宙の起源や根源物質の究

明といった文字通り目で見ることも手で触れることもできない対象を扱うのとは違い、結晶や結晶作用そのものはごくごくありふれた身近な現象であるからだ。だが、化学者たちの多くはいずれすべてが「必然的」に起きていることが証明される日がくると信じているのだ。また彼らは、新しい結晶の突然の出現と急速な広がりという現象について、従来の「感染」という説明で十分だと思っているのか、これに代わるもっと納得のゆく説明を考えようとはしていないようにみえる。おそらくあの密封容器の中で起きたグリセリンの結晶化も、異例の出来事というよりはむしろ何かのまちがい——容器の蓋が開いていたのではないかとか——とみなされているに違いない。

だが、この問題をまったく新しい角度から説き明かそうとする人物が現れた。イギリス生まれの少壮の生化学者ルパート・シェルドレイクである。彼は、結晶の形成は化学的・物理的相互作用から完全に説明できるはずだとする従来の機械論的考え方から思いきった飛躍をはかり、結晶の形態形成を促す未知の、〝目に見えない力〟の概念を打ち出したのである。この見えない作用を想定することによって結晶が示す不思議な現象は「感染」などという偶然の要因に頼らなくてもはるかに容易に説明がつくと彼はいう。そして、結晶の形態が化学物質の種類によって異なるのはこの見えない作用が同じ種類の化学物質に限定的に働くからであり、いいかえれば同じ種類の化学物質にだけ作用する〝見えない場〟が存在するからだというのだ。たとえばグリセリンの結晶形成が世界中で起きたのは結晶の種子が感染したからではなく、グリセリンという同じ種類の物質をつなぐ見えない場を通して結晶化のプロセスが伝播したからだということになる。密封容器のグリセリンが結晶できたのもそのためだ。

●形態形成場のメカニズム

シェルドレイクはこの見えない場を「形態形成場」と呼び、その作用は単に結晶のみならず自然界に存在する形態と名のつくものすべてに関与していると考えている。たとえば生物がその種に固有な形態を発現させるのも、ヒトにはヒトの、ネズミにはネズミの形態形成場があるからにほかならない。こういうとシェルドレイクの唱える形態形成場の概念はプラトンのいうイデアの焼きなおしではないかと思われる人もあろう。プラトンの思想をくむ伝統的な考え方では、物のとりうる形態はイデアとして初めから宇宙に存在するとしている。イデアはいわば潜在する原型であり、現実界に出現する形態に先行して存在するのである。しかしシェルドレイクの考える形態形成場は違う。彼はある新しい形態がこの世に初めて出現する理由を形態形成場で説明しようとは考えていない。創造の問題は別の次元の問題だと一線を画し、形態形成場説はあるきっかけで発現した新形態がなぜ繰り返し現れ、繰り返せば繰り返すほど発現しやすくなるのかという「反復」の問題を解説しているのだと彼はいう。従って形態形成場には始まりがある。ある形態が初めて現れたときにその形態形成場も同時に出現するのである。

グリセリンを例にとろう。グリセリンの結晶形成を促す形態形成場は輸送中の液体グリセリンの一

編者紹介

矢沢サイエンス・オフィス

科学雑誌『コズモ』の創刊編集長をつとめた矢沢深が1982年に設立。核エネルギー，宇宙開発，大規模プロジェクトなどの巨大科学，および物理学，天文学などの基礎科学の最先端について取材・執筆等の活動を行う。これまでに『巨大プロジェクト』『B－1 爆撃機』（講談社）などを制作したほか，最新科学論シリーズ（学研）では，『最終戦争論』『最新宇宙論』『最新脳科学』『最新恐竜論』『最新天体論』『最新宇宙技術論』『最新素粒子論』『最新アインシュタイン論』を制作。現在，核エネルギー，地球環境，生命と進化などのテーマに取り組んでいる。また訳書に，SDI（アメリカの戦略防衛構想）の技術的原理を詳述した『ビームディフェンス』，コンピュータの歴史と未来を扱った『第3の知性』（共に時事通信社）などがある。恐竜をテーマとしたCD－ROMを制作中。

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1954年生まれ。1980年から81年にかけて，東南アジアおよびインドを旅する。C＋Fコミュニケーションズ編『パラダイム・ブック』（日本実業出版社）で「物質編」を担当。

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1953年生まれ。1983年よりC＋Fコミュニケーションズのメンバーとなる。『パラダイム・ブック』で，編集リーダーを務め，『意識編』を担当。また，トランスパーソナル心理学の関係書の編集を主にてがけている。

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田崎宏美（たさき ひろみ）

1958年生まれ。日本エディタースクール第23期生。編集プロダクションを経て，C＋F研究所のメンバーとなる。『パラダイム・ブック』では『生命編』を担当。現在，中国気功に凝っている。

田中三彦（たなか みつひこ）

東京工業大学理工学部卒。科学・思想系の翻訳家，ジャーナリスト。おもな訳書にF・カプラ『タオ自然学』『ターニング・ポイント』（共訳，いずれも工作舎），C. スプレットナク＋F. カプラ『グリーン・ポリティックス』（岩土社）など。著書に『脳のデザイン』（福武書店）がある。

中村友紀夫（なかむら ゆきお）

1960年生まれ。1984年にC＋Fに編集スタッフとして参加。『パラダイム・ブック』で，『生命編』を担当。『トランスパーソナル宣言』（春秋社）の編集にも参加。

花嶺容子（はなづみ ようこ）

国際基督教大学仏文科卒。科学雑誌『コズモ』等の翻訳者を経て，矢沢サイエンス・オフィスのスタッフ。訳書に『ビーム・ディフェンス』（共訳，時事通信社）ほか。矢沢サイエンス・オフィス編集・最新科学論シリーズ（学習研究社）では，『最新素粒子論』等で翻訳・編集。現在，『最新核エネルギー論』『最新環境論』等を準備中。

三宅直人（みやけ なおと）

早稲田大学法学部卒。出版社勤務ののち，フリーライターとなる。著書に『台風の目は丸くない!?』（筑摩書房），『現代風俗史年表』（共著，河出書房新社），『巨大プロジェクト』（共著，講談社）。

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(57) Abstract

Process for the optical purification of the single enantiomers of some 2-sulphinyl-1H-benzimidazole derivatives and another structurally related sulphoxide from the respective enantiomerically enriched preparation thereof.

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A PROCESS FOR THE OPTICAL PURIFICATION OF ENANTIOMERICALLY ENRICHED BENZIMIDAZOLE DERIVATIVES

Technical field

The present invention relates to a process for the optical purification of enantiomerically enriched preparations of some 2-(pyridinylmethylsulphinyl)-1H-benzimidazole derivatives as well as another structurally related sulphoxide.

Prior art

There are a large number of patents and patent applications disclosing different substituted 2-(pyridinylmethylsulphinyl)-1H-benzimidazoles and structurally related sulphoxides. This class of compounds has properties making the compounds useful as inhibitors of gastric acid secretion. For example the compound (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole), having the generic name omeprazole, and therapeutically acceptable salts thereof are described in EP 5129. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. Other compounds also effective as gastric acid secretion inhibitors are the compounds 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole having the generic name lansoprazole, described in EP-A1-174726; 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole having the generic name pariprazole, described in EP 268956; 2-[[2-(N-isobutyl-N-methylamino)benzyl]sulphinyl]-1H-benzimidazole having the generic name leminoprazole, described in GB 2163747 and 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-

cyclohepta[b]pyridin-9-yl)sulphinyl]-1H-benzimidazole which is described in EP 434999.

These compounds omeprazole, lansoprazole, pariprazole and leminoprazole all have a stereogenic centre at the sulphur atom and thus exist as two stereoisomers (enantiomers). The compound 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)sulphinyl]-1H-benzimidazole has two stereogenic centers, one centre at the methine carbon atom adjacent to the sulphur atom and one at the sulphur atom. Thus, this compound exists as four stereoisomers (two pair of enantiomers). Even though the 2-(pyridinylmethylsulphinyl)-1H-benzimidazole class of chiral sulphoxides, including omeprazole, have been described in the scientific literature since the late seventies, there is not yet any efficient asymmetric process reported for the synthesis of the single enantiomers thereof. The single enantiomers of pharmacologically active compounds have met an increased interest in the last years because of improved pharmacokinetic and biological properties. Therefore, there is a need for a process that can be used in large scale for the preparation of the single enantiomers of omeprazole and of other optical pure omeprazole analogues. Generally, asymmetric processes for obtaining chiral sulphoxides afford optically active sulphoxides in enantiomerically enriched forms rather than in pure single enantiomeric forms unless the processes are enzymatic transformations or resolution methods. Therefore, there is also a need for a method that can be used in large scale for the enhancement of optical purity for enantiomerically enriched preparations of optically active omeprazole and other optically active omeprazole analogues.

Prior art discloses processes for resolution of different substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles. For example in DE 4035455 and WO 94/27988 such resolution processes are described. These processes involve reaction steps wherein a diastereomeric mixture is synthesised from the racemate of the corresponding substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles. The diastereomers are then separated and finally the separated

diastereomer is converted to the optically pure sulphoxide in a hydrolytic step. These resolution methods involving diastereomeric intermediates, suffer from at least three fundamental disadvantages namely:

1) The substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazole, as a racemic intermediate, has to be further processed in a couple of reaction steps before the single enantiomers can be obtained.

2) The resolution processes involve complicated separation steps.

3) There is a large waste of highly refined material when the unwanted stereoisomer, in the form of the opposite diastereomer, is discarded.

Further, prior art discloses for instance enantioselective synthesis of a 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazole derivative, namely the single enantiomers of the sulphoxide agent (5,7-dihydro-2-[[(4-methoxy-3-methyl -2-pyridinyl)methyl]-sulphinyl]-5,5,7,7-tetramethylindeno-[5,6-d]-imidazol-6-(1H)-one) see Euro. J. Biochem. 166 (1987) 453-459. This process is based on an enantioselective oxidation of the corresponding prochiral sulphide to said sulphoxide. The authors state that the crude product of the sulphoxide, showing an enantiomeric excess (e.e.) of about 30%, can be purified to optical pure sulphoxide [(e.e.) > 95%] by several steps of crystallisation. However, the yields and the number of crystallisation steps are not reported.
This proposed crystallization method is not suitable for the kind of substances according to the compounds of formula Ia- Ie in the present application.

Summary of the invention.

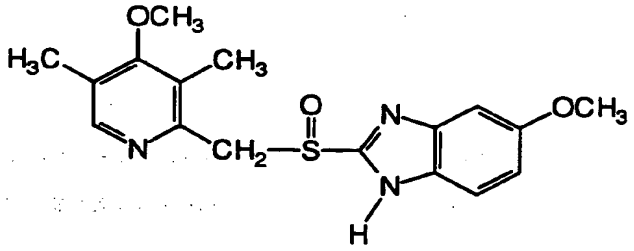
The object of the present invention is to provide a novel process for the enhancement of the optical purity (enantiomeric excess, e.e.) for enantiomerically

enriched preparations of omeprazole, lansoprazole, pariprazole, leminoprazole and 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)sulphinyl]-1H-benzimidazole. Surprisingly, the racemates of these compounds are very selectively precipitated from a solvent yielding the single enantiomers with an enhanced optical purity.

The process of the invention is defined in claim 1 and further preferred embodiments of the invention are disclosed in claims 2-9. Preferred compounds prepared by the new process are defined in claims 10-19.

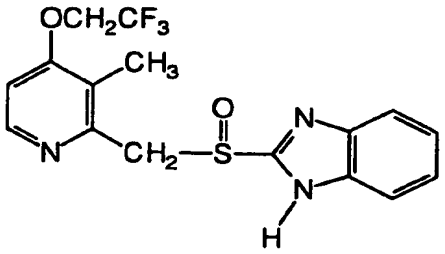
Detailed description of the invention.

The process of the present invention is characterised by the steps of treating an enantiomerically enriched preparation of optically active omeprazole of the formula Ia



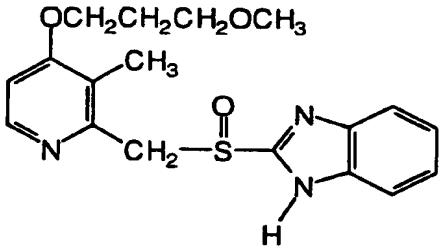
Ia

or of optically active lansoprazole of the formula Ib



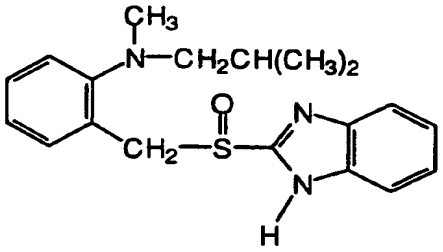
Ib

or of optically active pariprazole of the formula Ic



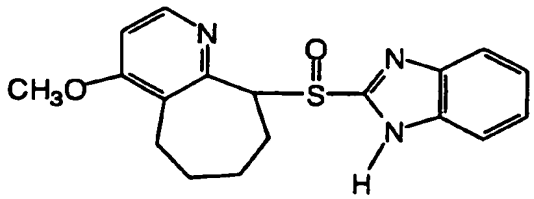
Ic

or of optically active leminoprazole of the formula Id



Id

or of optically active 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)sulphinyl]-1H-benzimidazole of the formula Ie



Ie

with a solvent from which the racemate is selectively precipitated. The precipitated benzimidazole derivative as a racemate, or as a racemate together with a small amount of the desired enantiomer is filtered off and the single enantiomer of the benzimidazole derivative, either as its (-)-enantiomer or as its (+)-enantiomer, with a dramatically enhanced optical purity is obtained by removing the solvent of the filtrate. The solvent is preferably removed by evaporation. The substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazole, to be treated in the process, is preferably omeprazole.

The precipitation is carried out in a protic or a non-protic solvent. The solvent facilitate the crystallisation and is necessary for the separation. The choice of solvent from which the racemate is precipitated is not essential for the process. Preferably the solvent is an organic solvent. A suitable organic solvent can be a ketone such as acetone or 2-butanone, or an ester such as ethyl acetate, or an alcohol such as ethanol, or a nitrile such as acetonitrile, or a hydrocarbon such as toluene. The solvent may also be an ether, an amide or any other organic solvent from which the racemate of the compounds according to formula Ia-Ie can be selectively precipitated. The solvent may also be a mixture of different organic solvents or a mixture of water and organic solvents. Preferably the solvent is one selected among acetone, toluen or acetonitril.

The temperature is not important for the process of the invention. However, if the temperature is too high the solubility increases, the selectivity decreases and the

compound decomposes. Therefore, room temperature is preferred, but also temperatures below room temperature are suitable.

Thus, a preferred feature of the process of the invention is that the racemates of the compounds according to formula Ia-Ie surprisingly are very selectively crystallised from an organic solvent. A dramatically enhancement of the enantiomeric excess of the (-)-enantiomer or the (+)-enantiomer of the present compounds is obtained in the mother liquor (filtrate), even after only one racemate crystallisation. Therefore, the process becomes highly effective. Consequently, the single enantiomers can be obtained with a very high enantiomeric excess even from optically impure preparations. This means that a high enantioselectivity is not essential for the asymmetric synthesis of the said optical active compounds, e.g. the asymmetric oxidation of corresponding prochiral sulphide. Thus, a broader scope of synthetic methods can be considered when choosing the most appropriate asymmetric synthesis processes for obtaining the compounds according to formula Ia-Ie. For example chemical yield, cost of reagents, reaction time and grade of dangerousness of handling reagents may thus be as important factors as enantioselectivety when making the choice of synthetic method.

The invention is illustrated more in detail by the following examples 1-16. The invention is illustrated together with an asymmetric synthesis in examples 7-9 .

EXAMPLES

The enantiomeric excess value in each example given below gives an indication of the relative amount of each enantiomer. The value is defined as the difference between the relative percentages for the two enantiomers. Thus, for example, when the percentage of the (-)-enantiomer of the sulphoxide is 97.5% and the percentage for the (+)-enantiomer is 2.5%, the enantiomeric excess for the (-)-enantiomer is 95%.

The enantiomeric composition of each sulphoxide was determined by chiral HPLC on either a Chiralpak AD Column or a Chiral AGP Column under the following conditions:

Compound of formula Ia.

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (100 ml), ethanol (100 ml) and acetic acid (10µl)
Flow	0.5 ml/min
Inj.vol.	50 µl
Wavelength	302 nm

Retention time for the (-)-enantiomer 4.0 min

Retention time for the (+)-enantiomer 5.8 min

Compound of formula Ib.

Column	Chiral AGP 100x4.0 mm
Eluent	Sodium phosfate buffer solution (pH 7.0), I=0.025 (500 ml) and acetonitrile (70 ml)
Flow	0.5 ml/min
Inj.vol.	20 µl
Wavelength	210 nm

Retention time for the (+)-enantiomer 6.2 min

Retention time for the (-)-enantiomer 7.2 min

Compound of formula Ic.

Column	Chiral AGP 100x4.0 mm
Eluent	Sodium phosfate buffer solution (pH 7.0), I=0.025 (430 ml) and acetonitrile (70 ml)
Flow	0.5 ml/min
Inj.vol.	20 µl
Wavelength	210 nm

Retention time for the (+)-enantiomer 4.1 min
Retention time for the (-)-enantiomer 6.8 min

Compound of formula Id.

Column Chiralpak AD 50x4.6 mm
Eluent iso-Hexane (200 ml) and ethanol (10 ml)
Flow 0.5 ml/min
Inj.vol. 50 µl
Wavelength 285 nm
Retention time for the (-)-enantiomer 9.0 min
Retention time for the (+)-enantiomer 9.8 min

Compound of formula Ie.

Column Chiralpak AD 50x4.6 mm
Eluent iso-Hexane (150 ml) and 2-propanol (50 ml)
Flow 0.4 ml/min
Inj.vol. 50 µl
Wavelength 285 nm
Retention time for the (-)-enantiomer of diasteremor A 6.9 min
Retention time for the (+)-enantiomer of diasteremor A 8.1 min
Retention time for the (+)-enantiomer of diasteremor B 8.8 min
Retention time for the (-)-enantiomer of diasteremor B 11.0 min
The first diastereomer of compound (Ie) eluted on straight phase (achiral silica gel, see below) is named diastereomer A and second as diastereomer B.

Example 1. Enhancement of optical purity from 60% e.e. to 98.4% e.e. for (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (-)-(Ia)

2.35 g of a mixture of the enantiomers of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (60% e.e., in favour of the (-)-

enantiomer) as a yellow syrup was dissolved in 20 ml of acetonitrile. Almost immediately the racemate as a solid appeared and after 30 minutes in a refrigerator this white solid was filtered off. The solvent of the filtrate was evaporated to yield 1.2 g of the (-)-enantiomer of omeprazole as a yellow syrup with an optical purity of 98.4% e.e.

Example 2. Enhancement of optical purity from 20% e.e to 91.4% e.e for (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (-)-(Ia)

2.35 g of a mixture of the enantiomers of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (20% e.e., in favour of the (-)-enantiomer) as a yellow syrup was dissolved in 20 ml of 2-butanone. Almost immediately the racemate as a solid appeared and after one hour in a refrigerator this white solid was filtered off. The solvent of the filtrate was evaporated to yield 0.48 g of the (-)-enantiomer of omeprazole as a yellow syrup with an optical purity of 91.4% e.e.

Example 3. Enhancement of optical purity from 50% e.e. to 97.3% e.e. for (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (-)-(Ia)

2.35 g of a mixture of the enantiomers of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (50% e.e., in favour of the (-)-enantiomer) as a yellow syrup was dissolved in 20 ml of acetone. Almost immediately the racemate as a solid appeared and after one hour in a refrigerator this white solid was filtered off. The solvent of the filtrate was evaporated to yield 1.0 g of the (-)-enantiomer of omeprazole as a yellow syrup with an optical purity of 97.3% e.e.

Example 4. Enhancement of optical purity from 80% e.e. to 95.4% e.e. for (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia)

2.35 g of a mixture of the enantiomers of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (80% e.e., in favour of the (+)-enantiomer) as a yellow syrup was dissolved in 20 ml of ethyl acetate. Almost immediately the racemate as a solid appeared and after one hour in a refrigerator this white solid was filtered off. The solvent of the filtrate was evaporated to yield 1.7 g of the (+)-enantiomer of omeprazole as a yellow syrup with an optical purity of 95.4% e.e.

Example 5. Enhancement of optical purity from 40% e.e. to 88.7% e.e. for (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia)

2.35 g of a mixture of the enantiomers of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (40% e.e., in favour of the (+)-enantiomer) as a yellow syrup was dissolved in 20 ml of ethanol. Almost immediately the racemate as a solid appeared and after one hour in a refrigerator this white solid was filtered off. The solvent of the filtrate was evaporated to yield 1.0 g of the (+)-enantiomer of omeprazole as a yellow syrup with an optical purity of 88.7% e.e.

Example 6. Enhancement of optical purity from 30% e.e. to 97.0% e.e. for (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia)

2.35 g of a mixture of the enantiomers of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole (30% e.e., in favour of the (+)-enantiomer) as a yellow syrup was dissolved in 20 ml of toluene. Almost

immediately the racemate as a solid appeared and after one hour in a refrigerator this white solid was filtered off. The solvent of the filtrate was evaporated to yield 0.62 g of the (+)-enantiomer of omeprazole as a yellow syrup with an optical purity of 97.0% e.e.

Example 7. Asymmetric synthesis followed by optical purification of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia)

A mixture of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole (0.47 g, 1.46 mmol), (3'S,2R)-(-)-N-(phenylsulphonyl)-(3,3-dichlorocamphoryl)oxaziridine (0.55 g, 1.46 mmol), triethylamine (0.07 ml, 0.5 mmol) and carbon tetrachloride 20 ml was stirred for 96 hours at ambient temperature. After removal of the solvent the residue was dissolved in methylene chloride (25 ml). The mixture was extracted with two portions of aqueous solutions of sodium hydroxide (0.1 M, 15 ml). The combined aqueous solutions were neutralised with an aqueous solution of ammonium chloride in the presence of methylene chloride. The phases were separated and the aqueous solution was extracted with two portions of methylene chloride. The combined organic solutions were dried over sodium sulphate and then the solvent was removed. The residue (200 mg, 40% e.e.) was dissolved in 2-butanone (3 ml) and the formed solid was filtered off. The solvent of the filtrate was evaporated to yield 0.11 g (22%) of the title compound with an optical purity of 94% e.e.

Example 8. Asymmetric synthesis followed by optical purification of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ia)

1.6 kg (5.0 mol) of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole was dissolved in 5.0 l of ethyl acetate. To the solution was added 31 ml (1.7 mol) of water. To the mixture was added 856 ml

(5.0 mol) of (-)-diethyl D-tartrate, 744 ml (2.5 mol) of titanium(IV) isopropoxide and 435 ml (2.5 mol) of diisopropylethylamine at room temperature. The addition of 830 ml (4.5 mol) cumene hydroperoxide was then performed at 30°C. After stirring for one hour at 30°C the reaction was complete. Chiral and achiral chromatographic analyses showed that the mixture consited of 71.4% sulphoxide with an enantiomeric excess (e.e.) of 72.9%. The mixture was cooled to 10°C and after addition of 1.7 l of isooctane, the product was extracted three times with an aqueous ammonia (12%) solution with a total volume of 10 l. The combined aqueous phases were neutralised by addition of 1.5 l of concentrated acetic acid in the presence of ethyl acetate (3 l). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 l). The solvent of the combined organic solutions was removed and at the end of the evaporation acetonitrile (1.5 l) was added to facilitate the removal of solvent. Acetone (2.5 l) was added to precipitate the racemate of omeprazole which was filtered off (254 g). HPLC-analyses (achiral and chiral columns) of the filtrate showed that this solution consited of 88% sulphoxide with an optical purity of 96.3% e.e. and thus the optical purity has been improved from 72.9% e.e. to 96.3% e.e. simply by one precipitation of racemic omeprazole. Further, a content analysis (HPLC) of the filtrate showed that the yield was 0.8 kg (46%). The (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole was not isolated in its neutral form but further processed to corresponding sodium salt.

Example 9. Asymmetric synthesis followed by optical purification of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia)

1.6 kg (5.0 mol) of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole was dissolved in 7.5 l of ethyl acetate. To the solution was added 31 ml (1.7 mol) water. To the mixture was added 856 ml (5.0 mol) of (+)-diethyl L-tartrate, 744 ml (2.5 mol) of titanium(IV) isopropoxide and 436 ml (2.5 mol) diisopropylethylamine at room temperature. The addition of 830

ml (4.5 mol) cumene hydroperoxide was then performed at 30°C. After stirring for one hour at 30°C the reaction was complete. Chiral and achiral chromatographic analyses showed that the mixture consited of 75% sulphoxide with an enantiomeric excess (e.e.) of 80%. The mixture was cooled to 10°C and after addition of 1.5 l of isooctane and ethyl acetate (0.5 l), the product was extracted three times with an aqueous ammonia (12%) solution with a total volume of 14 l. The combined aqueous phases were neutralised by addition of 1.5 l of concentrated acetic acid in the presence of ethyl acetate (4 l). The phases were separated and the aqueous phase was extracted with ethyl acetate (4 l). The solvent of the combined organic solutions was removed. Acetone (3.0 l) was added to precipitate the racemate of omeprazole which was filtered off. HPLC-analyses (achiral and chiral columns) of the filtrate showed that this solution consited of 90% sulphoxide with an optical purity of 95% e.e. and thus the optical purity has been improved from 80% e.e. to 95% e.e. simply by one precipitation of racemic omeprazole. Further, a content analysis (HPLC) of the filtrate showed that the yield was 1.0 kg (58%). The (+)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole was not isolated in its neutral form but further processed to corresponding sodium salt.

The starting material in form of enantiomerically enriched preparations for the optical purification of one of the compounds according to formulas Ib, Ic, Id or Ie is prepared as described in examples 8 and 9.

Example 10. Enhancement of the optical purity of two of the stereoisomers of 2-[(4-methoxy-6,7,8,9- tetrahydro-5H-cyclohepta[*b*]pyridin-9-yl)sulphinyl]-1H-benzimidazole, (Ie).

In the following example, the first diastereomer of the title compound eluted on straight phase (silica gel) is named diastereomer A and second as diastereomer B. The stereoisomeric composition of the title compound in a crude mixture as a syrup (0.25 g) was as follows; The ratio of diastereomers was 4:3 in favour of

diastereomer A. The optical purity of the (-)-enantiomer of diastereomer A was 76% e.e. and the optical purity of the (+)-enantiomer of diastereomer B was 68% e.e.

Separation of the diastereomers. A chromatographic preparation (methanol-methylene chloride 0 to 5%) afforded a separation of the two diastereomers. Thus, the (-)-enantiomer of diastereomer A was obtained as a syrup (0.145 g) with an optical purity of 77% e.e. The (+)-enantiomer of diastereomer B was also obtained as a syrup (0.085 g) with an optical purity of 68% e.e. , however, diastereomer B was contaminated with ca. 10% of diastereomer A.

Optical purification: The optical purity of the (-)-enantiomer of diastereomer A was enhanced by the addition of ca. 2 ml of acetonitrile to the enantiomerically enriched preparation of diastereomer A (0.145 g). After stirring over night, the formed precipitate (almost racemic diastereomer A) was filtered off and the solvent of the filtrate was removed by film evaporation. Thus, there was obtained 85 mg of the (-)-enantiomer of diastereomer A as a syrup with an optical purity of 88% e.e. The optical purity of the (+)-enantiomer of the diastereomer B was enhanced in a similar way. Thus, by addition of acetonitrile (2 ml) to the enantiomerically enriched preparation of diastereomer B (0.085 g) followed by stirring over night resulted in a precipitate which was filtered off. From the filtrate there was obtained 0.050 g of the (+)-enantiomer of diastereomer B with an optical purity of 95% e.e.

Example 11. Enhancement of the optical purity of (-)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (-)-(Ib).

1.2 g of a crude mixture of the title compound with an enantiomeric excess (e.e.) of 55% was treated with acetonitrile (a few ml) and there was obtained a precipitate that was removed by filtration. Evaporation of the filtrate afforded an oil with enhanced optical purity. Repeating this procedure a couple of times afforded 0.63 g of the desired compound as an oil with an optical purity of 99.5% e.e.

Example 12. Enhancement of the optical purity of (+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (+)-(Ib).

0.85 g of a crude mixture of the title compound with an enantiomeric excess (e.e.) of 46% was treated with acetonitrile (a few ml) and there was obtained a precipitate that was removed by filtration. Evaporation of the filtrate afforded an oil with enhanced optical purity. Repeating this procedure a couple of times afforded 0.31 g of the desired compound as an oil with an optical purity of 99.6% e.e.

Example 13. Enhancement of the optical purity of (-)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (-)-(Ic).

1.62 g of a crude mixture of the title compound with an enantiomeric excess (e.e.) of 90% was treated with acetonitrile (a few ml) and there was obtained a precipitate that could be removed by filtration. Concentrating the filtrate afforded 1.36 g of the title compound as an oil with an optical purity of 91.5% e.e.

Example 14. Enhancement of the optical purity of (+)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (+)-(Ic).

1.63 of a crude mixture of the title compound with an enantiomeric excess (e.e.) of 91% was treated with acetonitrile (a few ml) and there was obtained a precipitate that could be removed by filtration. Concentrating the filtrate afforded 1.1 g of the title compound as an oil with an optical purity of 96.0% e.e.

Example 15. Enhancement of the optical purity of (-)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]benzimidazole, (-)-(Id).

1.6 g of a crude mixture of the title compound with an enantiomeric excess (e.e.) of 92% was treated with a small amount of acetonitrile in order to enhance the

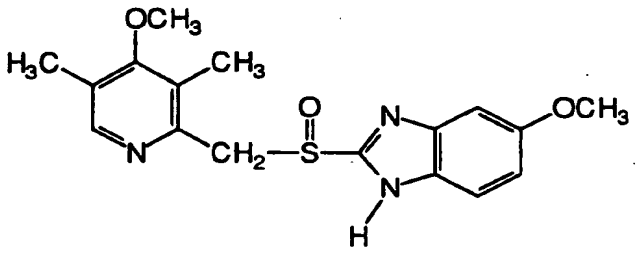
optical purity. A formed precipitate was removed by filtration. The solvent of the filtrate was removed by film evaporation and there was obtained 1.2 g of the desired compound as an oil. The optical purity of the material was 96% e.e. according to chiral HPLC.

Example 16. Enhancement of the optical purity of (+)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]benzimidazole, (+)-(Id).

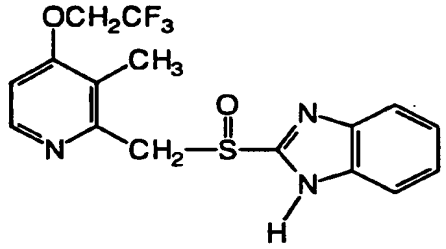
3.0 g of a crude mixture of the title compound (91% e.e.), contaminated with (-)-diethyl D-tartrate, was dissolved in 40 ml of a mixture of ethyl acetate and hexane (10% EtOAc). A formed precipitate (140 mg) was removed by filtration. The solvent of the filtrate was removed by film evaporation and the residue was purified by column chromatography (silica gel, EtOAc/Hexane 15:85). There was obtained 0.95 g of the title compound showing an optical purity of 96% e.e. according to chiral HPLC.

CLAIMS

1. A process for the optical purification of enantiomerically enriched preparations of one of the compounds according to formulas Ia, Ib, Ic, Id and Ie



Ia



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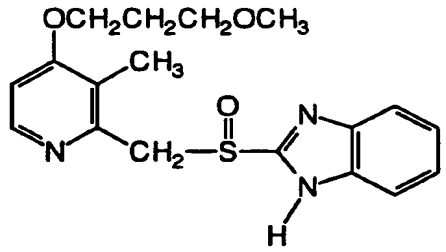

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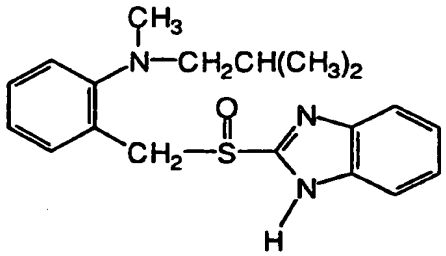

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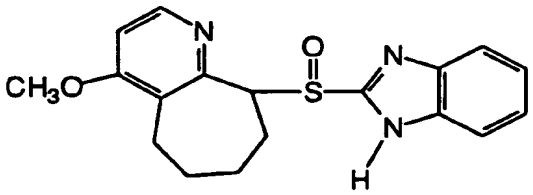


Ie

c h a r a c t e r i z e d in that an enantiomerically enriched preparation of a compound according to anyone of formula Ia-Ie, in favour of either its (+)- or (-)-enantiomer is treated with a solvent from which the racemate of said compound is selectively precipitated, whereby the precipitated racemate is filtered off followed by the removal of the solvent yielding the single enantiomer with an enhanced optical purity of the corresponding compound according to formula Ia-Ie.

2. A process according to claim 1 c h a r a c t e r i z e d in that optical purity of the (-)-enantiomer of the compound according to formula Ia is enhanced.

3. A process according to claim 1 c h a r a c t e r i z e d in that optical purity of the (+)-enantiomer of the compound according to formula Ia is enhanced.

4. A process according to claim 1 c h a r a c t e r i z e d in that the solvent is removed by evaporation.

5. A process according to claim 1 c h a r a c t e r i z e d in that the enantiomerically enriched preparation is treated with an organic solvent.

6. A process according to claim 1 c h a r a c t e r i z e d in that the enantiomerically enriched preparation is treated with a mixture of organic solvents.

7. A process according to claim 1 c h a r a c t e r i z e d in that the enantiomerically enriched preparation is treated with a mixture of water and one or more organic solvents.

8. A process according to claim 7 c h a r a c t e r i z e d in that the mixture of water and one or more organic solvents contains < 50% water.

9. A process according to claim 1 c h a r a c t e r i z e d in that the organic solvent is acetone, acetonitrile or toluen.

10. The compound (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole prepared by the process according to any of claims 1-9.

11. The compound (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole prepared by the process according to any of claims 1-9.

12. The compound (-)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole prepared by the process according to any of claims 1-9.

13. The compound (+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole prepared by the process according to any of claims 1-9.

14. The compound (-)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole.

15. The compound (+)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole.

16. The compound (-)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]-benzimidazole.

17. The compound (+)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]-benzimidazole.

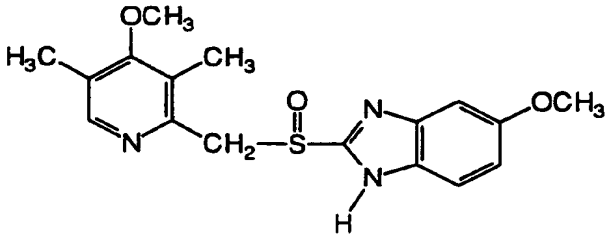
18. The compound (-)-2-[(4-methoxy-6,7,8,9- tetrahydro-5H-cyclohepta[*b*]pyridin-9-yl)sulphinyl]-1H-benzimidazole.

19. The compound (+)-2-[(4-methoxy-6,7,8,9- tetrahydro-5H-cyclohepta[*b*]pyridin-9-yl)sulphinyl]-1H-benzimidazole.

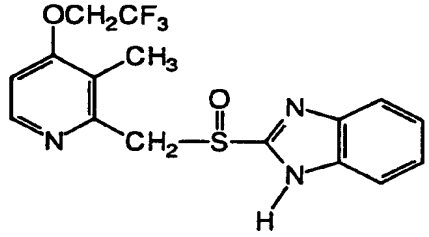
AMENDED CLAIMS

[received by the International Bureau on 27 November 1996 (27.11.96); original claims 10-19 amended; remaining claims unchanged (4 pages)]

1. A process for the optical purification of enantiomerically enriched preparations of one of the compounds according to formulas Ia, Ib, Ic, Id and Ie



Ia



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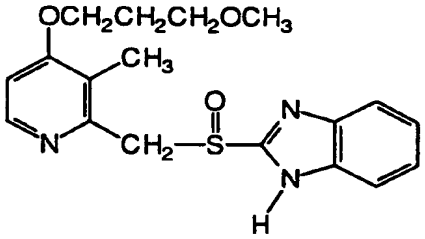
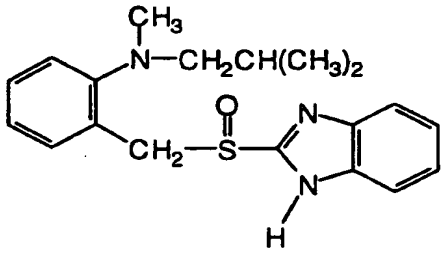


Ic



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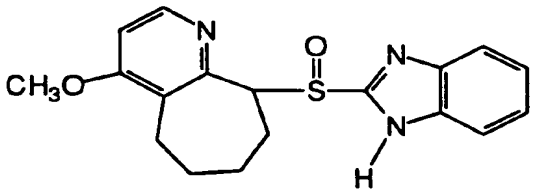

Ie

c h a r a c t e r i z e d in that an enantiomerically enriched preparation of a compound according to anyone of formula Ia-Ie, in favour of either its (+)- or (-)-enantiomer is treated with a solvent from which the racemate of said compound is selectively precipitated, whereby the precipitated racemate is filtered off followed by the removal of the solvent yielding the single enantiomer with an enhanced optical purity of the corresponding compound according to formula Ia-Ie.

2. A process according to claim 1 c h a r a c t e r i z e d in that optical purity of the (-)-enantiomer of the compound according to formula Ia is enhanced.

3. A process according to claim 1 c h a r a c t e r i z e d in that optical purity of the (+)-enantiomer of the compound according to formula Ia is enhanced.

4. A process according to claim 1 c h a r a c t e r i z e d in that the solvent is removed by evaporation.

5. A process according to claim 1 c h a r a c t e r i z e d in that the enantiomerically enriched preparation is treated with an organic solvent.

6. A process according to claim 1 c h a r a c t e r i z e d in that the enantiomerically enriched preparation is treated with a mixture of organic solvents.

7. A process according to claim 1 c h a r a c t e r i z e d in that the enantiomerically enriched preparation is treated with a mixture of water and one or more organic solvents.

8. A process according to claim 7 c h a r a c t e r i z e d in that the mixture of water and one or more organic solvents contains < 50% water.

9. A process according to claim 1 c h a r a c t e r i z e d in that the organic solvent is acetone, acetonitrile or toluen.

10. A process according to anyone of claims 1-9, wherein the prepared product is (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole.

11. A process according to anyone of claims 1-9, wherein the prepared product is (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole.

12. A process according to anyone of claims 1-9, wherein the prepared product is (-)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole.

13. A process according to anyone of claims 1-9, wherein the prepared product is (+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole.

14. A process according to anyone of claims 1-9, wherein the prepared product is (-)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole.

15. A process according to anyone of claims 1-9, wherein the prepared product is (+)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulphinyl]-1H-benzimidazole.

16. A process according to anyone of claims 1-9, wherein the prepared product is (-)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]-benzimidazole.

17. A process according to anyone of claims 1-9, wherein the prepared product is (+)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]-benzimidazole.

18. A process according to anyone of claims 1-9, wherein the prepared product is one of the single enantiomers of the more lipophilic diastereomer of 2-[(4-methoxy-6,7,8,9- tetrahydro-5H-cyclohepta[*b*]pyridin-9-yl)sulphinyl]-1H-benzimidazole.

19. A process according to anyone of claims 1-9, wherein the prepared product is one of the single enantiomers of the less lipophilic diastereomer of 2-[(4-methoxy-6,7,8,9- tetrahydro-5H-cyclohepta[*b*]pyridin-9-yl)sulphinyl]-1H-benzimidazole.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00841

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9515962 A1 (ASTRA AKTIEBOLAG), 15 June 1995 (15.06.95), see example 3 --	1-9
A	WO 9427988 A1 (ASTRA AKTIEBOLAG), 8 December 1994 (08.12.94), see example 1 --	1-9
X	DE 4035455 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 14 May 1992 (14.05.92) --	10-13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1996	08 -10- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00841

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. Pharm. Bull., Volume 42, No 3, 1994, Shin-ichi Yamada et al, "Syntheses and Antiulcer Activities of Novel 2-((6,7,8, 9-Tetrahydro-5H-cyclohepta(b)Pyridin-9-Yl)Sulfinyl) -1H-Benzimidazole Analogues" page 718 - page 720	18-19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

05/09/96

International application No.
PCT/SE 96/00841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9515962	15/06/95	AU-A- 1251295	27/06/95
		IL-D- 111707	00/00/00
		SE-D- 9304065	00/00/00
		ZA-A- 9409032	18/07/95
		SE-D- 9403728	00/00/00
WO-A1- 9427988	08/12/94	AU-A- 6902494	20/12/94
		CN-A- 1110477	18/10/95
		CZ-A- 9500202	18/10/95
		EP-A- 0652872	17/05/95
		FI-A- 950377	27/01/95
		HU-A- 71888	28/02/96
		HU-D- 9500247	00/00/00
		IL-D- 109684	00/00/00
		JP-T- 7509499	19/10/95
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		NO-A- 950263	24/01/95
		PL-A- 307261	15/05/95
		SI-A- 9420002	31/08/95
		SK-A- 10195	13/09/95
		ZA-A- 9403557	11/04/95
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		WO-A- 9208716	29/05/92

Reference Document 3

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INTERNATIONAL APPLICATION PUBLISHED U

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(30) Priority Data:
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(75) Inventors/Applicants *(for US only)*: LARSSON, Erik, Magnus [SE/SE]; Orrspelsvägen 33, S-161 39 Bromma (SE). STENHEDE, Urban, Jan [SE/SE]; Gabrielsvägen 38, S-151 50 Södertälje (SE). SÖRENSEN, Henrik [DK/SE]; Skogsvägen 13, S-435 38 Mölnlycke (SE). VON UNGE, Per, Oskar, Sverker [SE/SE]; Alvägen 4, S-430 33 Fjärås (SE). COTTON, Hanna, Kristina [SE/SE]; Siljansvägen 70, S-120 57 Årsta (SE).

(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

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(54) Title: PROCESS FOR SYNTHESIS OF SUBSTITUTED SULPHOXIDES

(57) Abstract

A novel process for enantioselective synthesis of single enantiomers of omeprazole or its alkaline salts, of other optically pure substituted 2-(2-pyridinylmethyl-sulphinyl)-1H-benzimidazoles as well as of other structurally related sulphoxides or their alkaline salts. The claimed process is an asymmetric oxidation of a pro-chiral sulphide to the single enantiomers or an enantiomerically enriched form of the corresponding sulphoxide. The application also claims the enantiomeric sulphoxide products produced by the process and their use in medicine.

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PROCESS FOR SYNTHESIS OF SUBSTITUTED SULPHOXIDES

Technical field

The present invention relates to a process for enantioselective synthesis of the single enantiomers of substituted sulphoxides or said compounds in an enantiomerically enriched form. Such substituted sulphoxides that are suitable for being prepared by the novel process are for examples the single enantiomers of omeprazole as well as the single enantiomers of other structurally related sulphoxides. The obtained products may thereafter be converted to pharmaceutically acceptable salts thereof by conventional processes. Further, the invention also relates to some new single enantiomeric compounds which can be prepared by the novel process and their use in medicine.

Background of the invention and prior art

There are a large number of patents and patent applications disclosing different substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles. This class of compounds has properties making the compounds useful as inhibitors of gastric acid secretion. For example the compound, (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole) with the generic name omeprazole, described in i.e. EP 5129, is useful as an antiulcer agent. Other compounds of interest are for instance the compounds with the generic names lansoprazole, pantoprazole, pariprazole and leminoprazole.

These compounds as well as structurally related sulphoxides, have a stereogenic centre at the sulphur atom and thus exist as two optical isomers, i.e. enantiomers. If there is another stereogenic centre in the molecule, these compounds can exist as pairs of enantiomers. Corresponding sulphides of such compounds which

already contain a stereogenic centre are not pro-chiral compounds, but chiral compounds. However, the sulphur atom in these compounds does not have asymmetry and therefore they are referred to as pro-chiral sulphides in respect of this invention.

Even though this class of chiral sulphoxides has been discussed in the scientific literature since the late seventies, there is not yet any efficient asymmetric process described for the synthesis of the single enantiomers thereof. The single enantiomers of pharmacologically active compounds have met an increased interest in the last years because of improved pharmacokinetic and biological properties. Therefore, there is a demand and need for an enantioselective process that can be used in large scale for the manufacture of the single enantiomers of pharmacologically active compounds, such as for instance optically pure, substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles.

There are processes for resolution of different substituted 2-(2-pyridinyl-methylsulphinyl)-1H-benzimidazoles disclosed in the prior art. Such resolution processes are for example described in DE 4035455 and WO 94/27988. These processes involve synthetic steps wherein a diastereomeric mixture is synthesised from the racemate of the corresponding substituted 2-(2-pyridinyl-methylsulphinyl)-1H-benzimidazoles. The diastereomers are then separated and finally one of the separated diastereomer is converted to the optically pure sulphoxide in a hydrolytic step.

These resolution methods involving diastereomeric intermediates, suffer from at least three fundamental disadvantages namely:

1) The substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazole, as a racemic intermediate, has to be further processed in a couple of reaction steps before the single enantiomers can be obtained.

2) The resolution processes described involve complicated separation steps.

3) There is a large waste of highly refined material when the unwanted stereoisomer, in the form of the opposite diastereomer, is separated and discarded.

Further, prior art describes for instance enantioselective synthesis of the single enantiomers of a sulphoxide agent Ro 18-5364, (5,7-dihydro-2-[[(4-methoxy-3-methyl-2-pyridinyl)methyl]-sulphinyl]-5,5,7,7-tetramethylindeno-[5,6-d]-imidazol-6-(1H)-one), See Euro. J. Biochem. 166 (1987) 453. The described process is based on an enantioselective oxidation of the corresponding prochiral sulphide to said sulphoxide. The experimental conditions used during the oxidation are stated to be in accordance with the asymmetric sulphide oxidation process developed by Kagan and co-workers (Pitchen, P.; Deshmukh, M.; Dunach, E.; Kagan, H. B. J. Am. Chem. Soc. 106 (1984), 8188). The authors report that the obtained crude product of the sulphoxide, showing an enantiomeric excess (e.e.) of about 30%, can be purified to an essentially optical pure sulphoxide [(e.e.) > 95%] by several steps of crystallisation. However, the yields and the number of crystallisation steps are not reported.

It is of interest to note that attempts of the Applicant to repeat the experimental conditions described and reported above, in the preparation of the single enantiomers of Ro 18-5364 afforded crude sulphoxide with an enantiomeric excess of only 16%.

In order to obtain the optically pure 2-(2-pyridinylmethyl-sulphinyl)-1H-benzimidazoles of interest, e.g. one of the single enantiomers of omeprazole, the Applicant obtained crude sulphoxides with a typical enantiomeric excess of about 5% or even lower with the above described method; See Reference Example A, below.

In the above mentioned process for asymmetric oxidations of sulphides to sulphoxides developed by Kagan and co-workers (J. Am. Chem. Soc. (1984) cited above), the oxidation is performed by using tert. butyl hydroperoxide as oxidising agent in the presence of one equivalent of a chiral complex obtained from $Ti(OiPr)_4$/(+)-or(-)-diethyl tartrate/water in the molar ratio of 1:2:1.

Kagan and co-workers reported that sulphoxide products with the highest enantioselectivity could be obtained when sulphides bearing two substituents of very different size were subjected to an asymmetric oxidation. For instance, when aryl methyl sulphides were subjected to oxidation, it was possible to obtain the aryl methyl sulphoxides in an enantiomeric excess (e.e.) of more than 90%.

However, when the substituents attached to the sulphur atom of the pro-chiral sulphide have a more equal size, a moderate or poor enantioselectivity was obtained. For instance, when benzyl p-tolyl sulphide is subject to oxidation under the conditions proposed by Kagan and co-workers, the e.e. observed is only 7%.

There have been attempts to improve the conditions for asymmetric oxidation of sulphides. For example, Kagan and co-workers (Zhao, S.; Samuel, O.; Kagan, H. B. Tetrahedron (1987), 43, 5135) found that a higher enantioselectivity generally could be obtained if the tert-butyl hydroperoxide in the system discussed above was replaced by cumene hydroperoxide in the oxidation of the sulphide. For instance an enantiomeric excess of 96% could be obtained in the asymmetric oxidation of methyl p-tolyl sulphide.

Thus, as a proposed method for asymmetric oxidation of sulphides, Kagan used cumene hydroperoxide with the system $Ti(O\text{-}iPr)_4$/diethyl tartrate/water (1:2:1) in methylene chloride at -23°C. The authors reported a decreased enantioselectivity when the amount of titanium reagent was lower than 0.5 equivalent. (See Tetrahedron (1987) cited above.)

Using this improved asymmetric oxidation process with one equivalent titanium reagent in order to obtain the optically pure 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles, e.g. one of the single enantiomers of omeprazole, the Applicant obtained a typical enantiomeric excess of about 10%; See Reference Example B, below.

The reaction conditions and their relevance in respect to the enantiomeric excess obtained for chiral sulphoxides in general, have also been discussed by Kagan and co-workers, See Synlett (1990), 643. For example a temperature of -20°C was found to be required for a high enantioselectivity and in some cases as low as -40°C was used by Kagan and co-workers to obtain the highest enantioselectivity. Further, the authors state that the enantioselectivity will be decreased when changing the organic solvent used in the oxidation from methylene chloride to for instance toluene. Methylene chloride and 1,2-dichloroethane are discussed as preferred solvents for the oxidation. It is to be noted that neither the low temperatures nor the proposed solvents are satisfactory from an industrial point of view.

Recently, a large scale asymmetric synthesis of an acylcholesterol acyltransferase (ACAT) inhibitor has been developed by Pitchen and co-workers (Pitchen, P; France, C. J.; McFarlane, I. M.; Newton, C. G.; Thompson, D. M. Tetrahedron Letters (1994), 35, 485). The discussed ACAT inhibitor, general named "compound RP 73163", is a chiral sulphoxide bearing one 4,5-diphenyl-2-imidazolyl group and one 5-(3,5-dimethyl-1-pyrazolyl)-1-pentyl group on the stereogenic center, i.e. the sulphur atom. However, the compound, which is not a substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazole type compound according to the present invention, has two large substituent groups attached to the stereogenic centre just as the compounds obtained in the present invention.

Initially, the corresponding prochiral sulphide of RP 73163, bearing these two large substituents on the sulphur atom, was oxidised using the above mentioned

asymmetric oxidation method proposed by Kagan (See Tetrahedron (1987) cited above). The prepared sulphoxide is reported to be obtained in a good chemical yield but the enantiomeric excess of the sulphoxide was 0% (racemic mixture). However, these discourraging results are not surprising for a chemist since in the literature the highest enantioselectivities for the titanium tartrate mediated reactions always have been reported in the case of oxidation of rigid (e.g. cyclic) sulphides or sulphides bearing two substituents of very different size. The authors conclude that the enantioselectivity for this type of oxidations is mainly governed by steric effects.

With respect of the information disclosed in published literature and in order to have a suitable prochiral substrate for an asymmetric oxidation, Pitchen and co-workers (See Tetrahedron Letters (1994) cited above) have decided to reduce the size of one of the substituents attached on the sulphur atom in the sulphide. An intermediate of choice for such a process may be a N-protected 4,5-diphenyl-2-imidazolyl methyl sulphide which after oxidation is obtained as the corresponding sulphoxide. The enantiomeric excess of the formed sulphoxides is in the range of 98-99%. However, the synthetic route becomes more complicated using an intermediate than the originally method proposed for the asymmetric oxidition of 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenyl imidazole. Starting from 4,5-diphenyl-2-imidazolethiol, the synthetic route has to include the following synthetic steps:

1) Methylation of the mercapto group.

2) Attaching a protective group to one of the nitrogen atoms in the imidazole moiety.

3) Asymmetric oxidation of the sulphide to a sulphoxide.

4) Reacting the obtained methyl sulphoxide derivative with a strong base, such as lithium diisopropyl amide (LDA), in order to abstract a proton from the methyl group.

5) Alkylating the lithium salt of the methyl sulphoxide derivative with 4-chloro-1-iodobutane giving a 5-chloropentyl sulphoxide derivative.

6) Attaching the pyrazolyl group to the n-pentyl chain.

7) Removing the protective group.

It is obvious that the proposed complicated approach by optimising the size of the substituents is not suitable for preparation, especially not in a large scale.

It should be noted that the process according to the present invention applied to the pro-chiral sulphide of RP 73163, surprisingly gives RP 73163 in an enantiomeric excess of > 85-90%, See Reference Examples E and F, below.

The prior art literature does not disclose nor propose a suitable enantioselective process which can be used in large scale for obtaining the single enantiomers of 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles. Therefore, there is still a long-felt demand for such an enantioselective process for the manufacture of substituted optically pure 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles as well as other structurally related sulphoxides.

Brief description of the invention

The present invention provides a novel process for enantioselective synthesis of the single enantiomers of omeprazole, of other optically pure substituted 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazoles as well as of other structurally related sulphoxides, in which process a surprisingly high enantioselectivity is obtained. The novel process is characterized in that a pro-chiral sulphide is oxidised asymmetrically into a single enantiomer or an enantiomerically enriched form of the corresponding sulphoxide. This novel asymmetric oxidation surprisingly makes it possible to obtain the compounds of interest with an extremely high enantiomeric excess, even if the corresponding pro-chiral sulphide has substituents on the sulphur atom of approximately the same size. The process is simple with one step of reaction making the process suitable for large scale production of enantiomeric compounds in a high yield and with a high enantiomeric excess.

The expressions "pro-chiral sulphide(s)" are used for the sulphides of the corresponding sulphoxides suitable for being prepared by the novel process according to the present invention. If the corresponding sulphide already contains a stereogenic centre in the molecule, such a sulphide is not a pro-chiral compound, but a chiral compound. Since the sulphur atom of the sulphides does not have asymmetry such a compound is referred to as a pro-chiral sulphide in the present specification and appending claims.

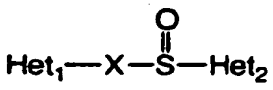
The present invention also provides optically pure compounds prepared in accordance with the claimed process and some novel single enantiomeric compounds.

The process of the invention is defined in claim 1 and some alternative processes are described in the independent claims 2 - 4. The subclaims 5 - 23 define some

specifically preferred embodiments of the invention, and preferred products prepared by the new process are defined in claims 24 - 33.

Detailed description of the invention.

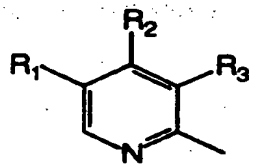
The present invention provides a novel method of preparing a sulphoxide of formula I either as a single enantiomer or in an enantiomerically enriched form:



I

wherein

Het_1 is



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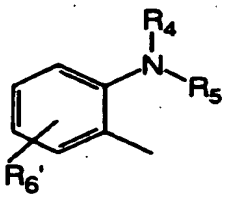
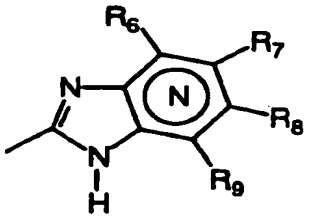


Het_2 is



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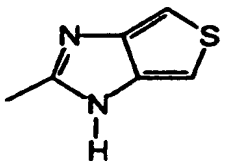
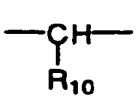


and X is



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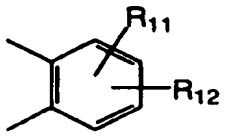


wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optionally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

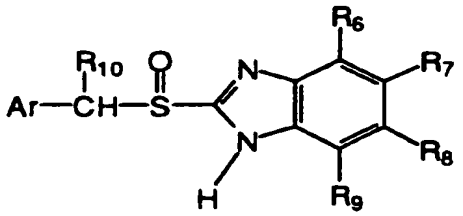
R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen and alkyl.

In the above definitions alkyl groups, alkoxy groups and moities thereof may be branched or straight C_1-C_9-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl.

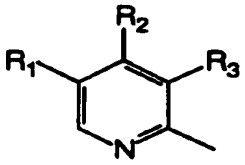
Preferably, the sulphoxides prepared by the novel method are sulphoxides of formula I' either as a single enantiomer or in an enantimerically enriched form:



(I')

wherein

Ar is



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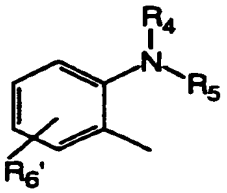
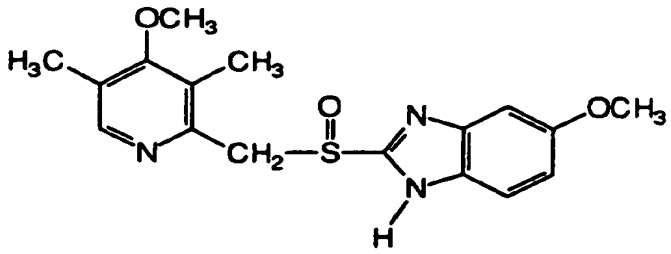


and R_1 - R_{10} are as defined above in connection with formula I.

Most preferably the sulphoxides prepared by the novel process are sulphoxides of any of the formulas Ia to Ih either as a single enantiomer or in an enantimerically enriched form:



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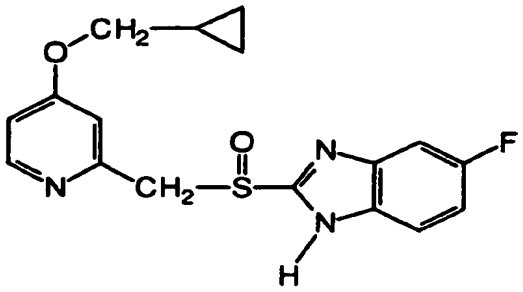

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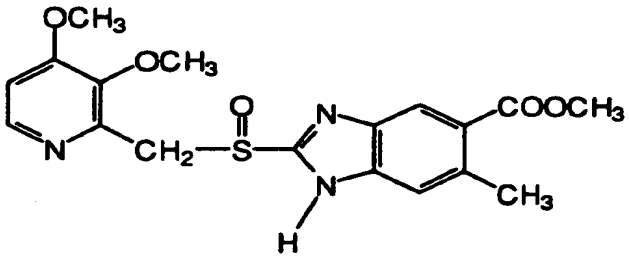

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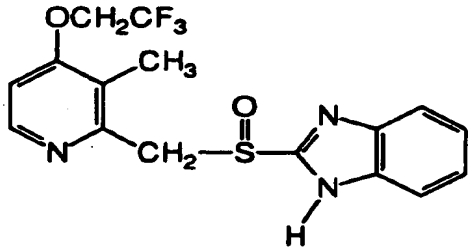

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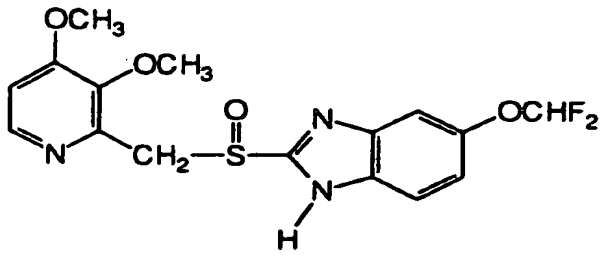

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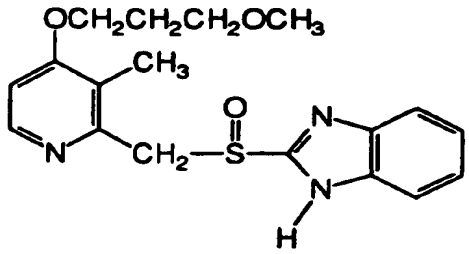

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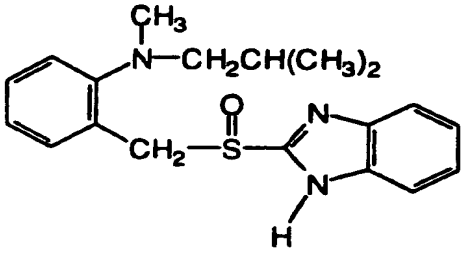

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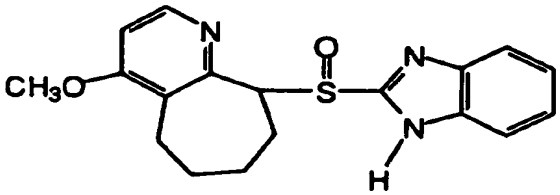


(Ih)

The compounds defined by the above formulas I, I' and Ia - Ih may be converted to pharmaceutically acceptable salts thereof by conventional methods.

The process of the present invention is characterized by an asymmetric oxidation in an organic solvent of a pro-chiral sulphide according to formula II

$$Het_1—X—S—Het_2 \qquad II$$

wherein Het_1 and Het_2 are as defined above

with an oxidising agent and a chiral titanium complex, optionally in the presence of a base.

According to one aspect of the invention the asymmetric oxidation is carried out in the presence of a base.

Alternatively, the oxidation can be carried out in the absence of a base if the preparation of the chiral titanium complex is performed in a specific way with respect to the order of addition, preparation temperature and/or preparation time.

Thus, according to one preferred aspect of the invention the preparation of the chiral titanium complex is performed in the presence of the pro-chiral sulphide, i e the pro-chiral sulphide is loaded into the reaction vessel before the components used for the preparation of the chiral titanium complex are loaded.

According to another preferred aspect of the invention the preparation of the chiral titanium complex is performed during an elevated temperature and/or during a prolonged preparation time.

According to still another preferred aspect of the invention the preparation of the chiral titanium complex is performed during an elevated temperature and/or

during a prolonged preparation time and in the presence of the pro-chiral sulphide.

According to the most preferred aspect of the invention, the asymmetric oxidation is carried out in the presence of a base and the preparation of the chiral titanium complex is performed during an elevated temperature and/or during a prolonged preparation time and in the presence of the pro-chiral sulphide.

The oxidation is carried out in an organic solvent. Surprisingly, the solvent is not as essential for the enantioselectivity of the oxidation, as reported by Kagan and co-workers. The solvent can be chosen with respect to suitable conditions from an industrial point of view as well as environmental aspects. Suitable organic solvents are for instance toluene, ethyl acetate, methyl ethyl ketone, methyl isobutyl ketone, diethyl carbonate, tert. butyl methyl ether, tetra hydrofurane, methylene chloride and the like. From an environmental point of view non-chlorinated solvents are preferred.

The oxidation is preferably carried out in an organic solvent at room temperature or just above room temperature, e g between 20 - 40° C. Surprisingly, the process does not require a temperature below - 20 ° C, as described by Kagan and co-worker as essential for good enantioselectivity. Such a low temperature results in long reaction times. However, if the reaction time is variated a reaction temperature may be chosen below as well as above the preferred temperatures 20 - 40° C. A suitable temperature range is limited only depending on the decomposition of the compounds, and that the reaction time is dramatically shorter at room temperature than at -20° C since the sulphides of interest are oxidised very slowly at such a low temperature.

An oxidising agent suitable for the novel asymmetric oxidation may be a hydroperoxide, such as for example tert.-butylhydroperoxide or cumene hydroperoxide, preferably the latter.

The titanium complex suitable for catalysing the process of the invention is prepared from a chiral ligand and a titanium(IV) compound such as preferably titanium(IV)alkoxide, and optionally in the presence of water. An especially preferred titanium(IV)alkoxide is titanium(IV)isopropoxide or -propoxide. The amount of the chiral titanium complex is not critical. An amount of less than approximately 0.50 equivalents is preferred and an especially preferred amount is 0.05 -0.30 equivalents. Surprisingly, even very low amounts of complex, such as for instance 0.04 equivalents may be used in the processes according to the present invention with excellent result.

The titanium complex may also be prepared by reacting titanium tetra chloride with a chiral ligand in the presence of a base.

The chiral ligand used in the preparation of the titanium complex is preferably a chiral alcohol such as a chiral diol. The diol may be a branched or unbranched alkyl diol, or an aromatic diol. Preferred chiral diols are esters or tartaric acid, especially (+)-diethyl L-tartrate or (-)-diethyl D-tartrate are preferred.

As discussed above and more in detail below, the chiral titanium complex may be prepared in the presence of the pro-chiral sulphide or before the pro-chiral sulphide is added to the reaction vessel.

As mentioned above, according to one aspect of the invention, the oxidation is carried out in the presence of a base. A surprisingly high enantioselectivity is observed when a base is present during the oxidation. This noteworthy high enantioselectivity is observed even though the substrates are pro-chiral sulphides with substituents on the sulphur atom having approximately the same size.

The base may be an inorganic or an organic base, such as for instance a hydrogen carbonate, an amide or an amine. Amine includes a guanidine or an amidine.

Organic bases are preferred and especially suitable bases are amines, preferably triethylamine or N,N-diisopropylethylamine. The amount of base added to the reaction mixture is not critical but should be adjusted with respect to the reaction mixture.

This specific feature of adding a base to the reaction mixture in order to enhance the enantioselectivity of the oxidation is exemplified by two experiments with 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole used as the pro-chiral sulphide for the reaction. See Reference Examples D and E. The reaction conditions are the same in both experiment, except for the addition of a base to the reaction mixture in one of the experiments. Reference Example D is performed in accordance with claim 1 of the present invention, i e the asymmetric oxidation is performed in the presence of a base. Reference Example C is performed in the absence of a base without any alteration of the process parameters. The results show that the oxidation without any addition of a base according to Reference Example C affords a sulphoxide product with an enantiomeric excess (e.e.) of 23%, while the oxidation in the presence of a base, such as diisopropylethylamine, according to Reference Example D affords a sulphoxide product with an enantiomeric excess of 78%.

Alternatively, the process of the invention can be carried out in the absence of a base. Under such conditions the processes for preparation of the chiral titanium complex are essential.

The preparation of the chiral titanium complex is preferably performed in the presence of the pro-chiral sulphide. By alter the order of addition compared to the processes disclosed in prior art the enantioselectivety of the oxidation is surprisingly enhanced.

Other essential features in the preparation of the chiral titanium complex is that the preparation of the complex is performed during an elevated temperature

and/or during a prolonged time. With an elevated temperature is meant a temperature above room temperature, such as for instance 30 - 70 ° C, preferably 40 - 60 ° C. A prolonged preparation time is a period of time longer that approximately 20 minutes, preferably 1 - 5 hours. A suitable period of time for the preparation step depends on the preparation temperature and of the pro-chiral sulphide, optionally present during the preparation of the chiral titanium complex.

The products formed during the oxidation reaction may be extracted with an aqueous solution of ammonia or another N-containing base to avoid precipitation and/or formation of insoluble titanium salts. The aqueous phase is separated from the organic phase of the obtained mixture and the isolated aqueous phase is neutralised by the addition of a neutralising agent resulting in a protonation of the optically active sulphoxide.

Thus, another preferred feature of the process of the invention is that the titanium salts which may be formed during the process can be kept in solution by the addition of an aqueous ammonia solution. The conventional procedure described in the literature for washing out titanium salts is a treatment of the reaction mixture with water or aqueous sodium hydroxide solutions resulting in the formation of a gel which is very difficult to filter off. Another procedure for washing out the titanium salts described in the prior art, is for instance to use 1M HCl, proposed in the work by Pitchen and co-workers (Tetrahedron Letters (1994) cited above). This procedure cannot be used for products being acid labile, such as for instance 2-(2-pyridinyl-methylsulphinyl)-1H-benzimidazoles which are destroyed almost immediately in acidic solutions.

The obtained crude product may be extracted in an organic solvent. It may also be crystallised in an organic or aqueous solvent resulting in an optically pure product, such as for instance one of the single enantiomers of a 2-(2-pyridinylmethylsulphinyl)-1H-benzimidazole in the neutral form. The acidic

proton in the benzimidazole moiety may be abstracted by treating the crude product with a base such as NaOH followed by crystallisation of the formed salt in a solvent which may result in a product with an improved optical purity.

The invention is illustrated more in detail by the following examples.

EXAMPLES

Example 1.

Asymmetric synthesis of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole sodium salt, (-)-(Ia)-Na

59 g (180 mmol) of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole was dissolved in 200 ml ethyl acetate. To the solution was added 0.3 ml (17 mmol) water. To the mixture was added 37 g (180 mmol) (+)-diethyl L-tartrate, 25 g (90 mmol) titanium(IV) isopropoxide and 16 ml (90 mmol) diisopropylethylamine at room temperature. The addition of 30 ml (160 mmol) cumene hydroperoxide (80%) was then performed over a period of 90 minutes at 34°C. After cooling to room temperature for 120 minutes a small sample of the mixture was taken for chiral and achiral chromatographic analyses. The mixture consisted of 82% sulphoxide with an enantiomeric excess (e.e.) of 87%. The mixture was diluted with 60 ml isooctane and 40 ml ethyl acetate whereupon the product was extracted three times with an aqueous ammonia (12%) solution with a total volume of 480 ml. The combined aqueous phases were neutralised by addition of 50 ml concentrated acetic acid. Thereafter, the workup procedure employed extraction, evaporation, sodium hydroxide addition and crystallisation procedures yielding 32.7 g of the title compound with a purity of 95.2% (achiral analysis) and with an enantiomeric excess (e.e.) of 99.8% (chiral analysis).The overall yield was 47.2%.

Example 2.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia)

Titanium(IV) isopropoxide (1.3 ml, 4.5 mmol) and water (41 µl, 2.3 mmol) were added with stirring to a solution of (+)-diethyl L-tartrate (1.5 ml, 9.0 mmol) dissolved in toluene (10 ml). The mixture was stirred for 20 minutes at room temperature and then 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.0 g, 9 mmol) and diisopropylethyl amine (0.45 ml, 2.6 mmol) were introduced. At 30 °C cumene hydroperoxide (tech, 80%, 1.8 ml, 9.9 mmol) was added. After 3 h at 30 °C the mixture consisted of 2.1% sulphide, 8.8% sulphone and 86.8% sulphoxide with an enantiomeric excess of 74%.

Example 3.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia).

To a mixture of (+)-diethyl L-tartrate (4.2 g, 20 mmol), titanium(IV) isopropoxide (2.9 g, 10 mmol) and ethyl acetate was added water (0.18 ml, 10 mmol). The solution was stirred for 20 minutes whereupon 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole (3,4 g, 10 mmol) was added together with $KHCO_3$ (0.31 g, 3.1 mmol) and cumene hydroperoxide (1.8 ml, 10 mmol). The addition was performed at room temperature. HPLC analysis was performed after 1.5 hours which showed 63.3% sulphoxide with an enantiomeric excess of 38.9%.

Example 4.

Asymmetric synthesis of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole sodium salt, (-)-(Ia)-Na

Water (0.45 ml, 25 mmol) was added at room temperature to a solution of (+)-diethyl L-tartrate (8.5 ml, 50 mmol) and titanium (IV) isopropoxide (7.4 ml, 25 mmol) in 250 ml methylene chloride. After 20 minutes 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole (8.2 g, 25 mmol) and diisopropylethylamine (1.3 ml, 7 mmol) were added and the solution was cooled to -20°C. After addition of cumene hydroperoxide (5.1 ml 80% soln, 28 mmol) the reaction mixture was kept at +2 °C for 66 h. Workup by addition of 2x125 ml sodium hydroxide solution was followed by neutralisation of the aqueous phase with ammonium chloride. Thereafter, the workup procedure employed extraction, evaporation, flash chromatography, sodium hydroxide addition and crystallisation procedures yielding 1.23 g (13.4%) g of the title compound with a an enantiomeric excess (e.e.) of 99.8% (chiral analysis).

Example 5.

Asymmetric synthesis of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (-)-(Ia).

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (4.0 g, 12.1 mmol) was suspended in toluene (12 ml) (-)-Diethyl D-tartrate (0.17 ml, 1.0 mmol) and titanium(IV) isopropoxide (0.15 ml, 0.50 mmol) were added with stirring at 50°C. The mixture was stirred at 50°C for 50 minutes and then N,N-diisopropylethylamine (0.085 ml, 0.50 mmol) was added at ca. 30°C. Then, cumene hydroperoxide (83%, 2.1 ml, 11.9 mmol) was added and the mixture was stirred for 15 minutes at 30°C. The crude mixture was shown to consist of 3.6% sulphide, 2.7% sulphone and 93% sulphoxide with an optical purity of 91% e.e. The product was not isolated.

Example 6.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia).

(+)-Diethyl L-tartrate (1.71 ml, 10 mmol) and titanium(IV) isopropoxide (1.5 ml, 5 mmol) were dissolved in methylene chloride (50 ml). Water (90 µl, 5 mmol) was added with stirring and the resultant mixture was heated to reflux for one hour. The mixture was cooled to room temperature. Thereafter, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.65 g, 5 mmol) and cumene hydroperoxide (80%, 1.05 g, 5.5 mmol) were added at room temperature. The solution was stirred at room temperature for 90 minutes. The crude mixture was shown to consist of 42.8% sulphide, 4.1% sulphone and 48.3% sulphoxide with an optical purity of 43% e.e. The product was not isolated.

Example 7.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia).

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.65 g, 5 mmol) was dissolved in methylene chloride (50 ml). (+)-Diethyl L-tartrate (1.71 ml, 10 mmol), titanium(IV) isopropoxide (1.5 ml, 5 mmol) and water (90 µl, 5 mmol) were added with stirring. The resultant mixture was stirred at room temperature for 20 minutes. Thereafter, cumene hydroperoxide (80%, 1.05 g, 5.5 mmol) were added at room temperature and the solution was stirred at room temperature for 90 minutes. The crude mixture was shown to consist of 38.9% sulphide, 8.4% sulphone and 47.6% sulphoxide with an optical purity of 32% e.e. The product was not isolated.

Example 8.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole, (+)-(Ia).

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (0.5 g, 1.5 mmol) was suspended in toluene (2.5 ml). Water 9.2 µl (0.5 mmol), (+)-Diethyl L-tartrate (0.39 ml, 2.3 mmol) and titanium(IV) isopropoxide (0.27 ml, 0.91 mmol) were added at 50°C. The mixture was warmed at 50°C for 90 minutes whereupon 0.25 ml of the solution was transferred to a test-tube. To this tube was then added 25 µl of cumene hydroperoxide (80%) and almost immediately thereafter this mixture consisted of 41% desired sulphoxide with an optical purity of 69.5% ee. The product was not isolated.

Example 9.

Asymmetric synthesis of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole sodium salt, (-)-(Ia)-Na

1.6 kg (5.0 mol) of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole was dissolved in 7.5 l ethyl acetate. To the solution was added 31 ml (1.7 mol) water. To the mixture was added 860 ml (5.0 mol) (+)-diethyl L-tartrate, 740 ml (2.5 mol) titanium(IV) isopropoxide and 430 ml (2.5 mol) diisopropylethylamine at room temperature. The addition of 830 ml (4.5 mol) cumene hydroperoxide (80%) was then performed over a period of 50 minutes at 30°C. After an additional hour at 30°C the reaction was completed. Chiral and achiral chromatographic analyses show that the mixture consists of 75% sulphoxide with an enantiomeric excess (e.e.) of 80%, 19% unreacted sulphide and 3.8% sulphone. The mixture was cooled to 10°C and after addition of 1.5 l isooctane and 0.5 l ethyl acetate, the product was extracted three times with an aqueous ammonia (12%) solution with a total volume of 14 l. The combined aqueous phases were neutralised by addition of 1.5 l concentrated acetic acid.

Thereafter, the workup procedure employed extraction, evaporation, sodium hydroxide addition and crystallisation procedures yielding 0.80 kg of the title compound with a purity of 99.3% (achiral analysis) and with an enantiomeric excess (e.e.) of 99.8% (chiral analysis).The overall yield was 44%.

Example 10.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole sodium salt, (+)-(Ia)-Na

1.6 kg (5.0 mol) of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole was dissolved in 6.1 l ethyl acetate. To the solution was added 31 ml (1.7 mol) water. To the mixture was added 860 ml (5.0 mol) (-)-diethyl D-tartrate, 740 ml (2.5 mol) titanium(IV) isopropoxide and 430 ml (2.5 mol) diisopropylethylamine at room temperature. The addition of 830 ml (4.5 mol) cumene hydroperoxide (80%) was then performed over a period of 25 minutes at 30°C. After additional 30 minutes at 30°C the reaction was completed. Chiral and achiral chromatographic analyses show that the mixture consists of 71% sulphoxide with an enantiomeric excess (e.e.) of 73%. The mixture was cooled to 10°C and after addition of 1.7 l isooctane, the product was extracted three times with an aqueous ammonia (12%) solution with a total volume of 14 l. The combined aqueous phases were neutralised by addition of 1.5 l concentrated acetic acid. Thereafter, the workup procedure employed extraction, evaporation, sodium hydroxide addition and crystallisation procedures yielding 0.45 kg of the title compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess (e.e.) of 99.8% (chiral analysis). The overall yield was 24.6%.

Example 11.

Asymmetric synthesis of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole sodium salt, (+)-(Ia).

6.2 kg (18.8 mol) Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in toluene suspension (25 l) was heated to 54°C. Water (44 ml, 2.4 mol), (-)-diethyl D-tartrate (2.35 kg, 11.4 mol) and titanium(IV) isopropoxide (1.60 kg, 5.6 mol) were added with stirring and then the mixture was stirred at 54°C for 50 minutes. The temperature was adjusted to 30°C whereupon N,N-diisopropylethylamine (720 g, 5.6 mol) was added to the solution. Then, cumene hydroperoxide (83.5%, 3.30 kg, 18.2 mol) was added and the mixture was stirred for one hour at 30°C. The crude mixture was shown to consist of 7% sulphide, 1.2% sulphone and 90.6% sulphoxide with an optical purity of 94.3% e.e. Aqueous ammonia (12.5%, 20 l) was added. The solution was extracted three times with aqueous ammonia (3x20 l). To the combined aqueous layers was added methyl isobutyl ketone (9 l). The aqueous layer was pH-adjusted with acetic acid and then the layers were separated. The aqueous layer was extracted with an additional portion of methyl isobutyl ketone (9 l).To make the sodium salt, to the solution was added an aqueous solution of NaOH (49.6%, 1.07 kg, 13.2 mol) and acetonitrile (70 l). The solution was concentrated and the product started to crystallize. 3.83 kg of the (+)-enantiomer of the sodium salt of omeprazole was isolated with an optical purity of 99.6% e.e.

Example 12.

Asymmetric synthesis of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ib)

Titanium (IV) isopropoxide (8.9 ml, 30 mmol) and water (0.54 ml, 30 mmol) was added with stirring to a mixture of (+)-diethyl L-tartrate (10.3 ml, 60 mmol) and methylene chloride (60 ml). The solution was stirred for 30 minutes at room

temperature and then 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methylthio]-1H-benzimidazole (9.9 g, 30 mmol) and diisopropylethylamine (1.50 ml, 8.7 mmol) were introduced. At room temperature cumene hydroperoxide (tech, 80%, 6.0 ml, 33 mmol) was added. After 3 h at room temperature the mixture consisted of a crude sulphoxide with an enantiomeric excess (e.e.) of 60%. After purification on silica gel with methanol/methylene chloride as eluent followed by repeated crystallisations from ethanol there was obtained 1.1 g (11%) of the title compound with an enantiomeric excess of 98.6%.

Example 13.

Asymmetric synthesis of (-)-5-fluoro-2-[[(4-cyclopropyl-methoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ib).

5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.0 g, 45 mmol) was suspended in toluene (60 ml). Water (34 µl, 1.9 mmol), (-)-diethyl D-tartrate (1.60 ml, 9.3 mmol) and titanium(IV) isopropoxide (1.3 ml, 4.5 mmol) were added with stirring at 50°C. The mixture was stirred at 40°C for 50 minutes and then N,N-diisopropylethylamine (0.79 ml, 4.5 mmol) was added. The temperature was adjusted to 35°C and then cumene hydroperoxide (83%, 8.1 ml, 45 mmol) was added. The mixture was stirred for 30 minutes at 35°C. The crude mixture was shown to consist of 6.5% sulphide, 2.7% sulphone and 90% sulphoxide with an optical purity of 87.7% e.e. The product started to crystallize during the oxidation and was isolated from the reaction mixture by filtration. There was obtained 11.7 g of the desired product with an optical purity of 98.8% e.e. The material was also shown to consist of 2.2% sulphide and 0.9% of sulphone. Yield: 71.2%.

Example 14.

Asymmetric synthesis of (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ib).

5.0 g (15 mmol) of 5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole was mixed with toluene (30 ml). To the mixture was added 32 µl (1.8 mmol) of water, 1.3 ml (7.6 mmol) of (-)-diethyl D-tartrate and 0.90 ml (3.0 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled 30°C. Thereafter, 2.8 ml (15 mmol) of cumene hydroperoxide (80%) was added to the solution. The mixture was stirred for one hour at 30°C and thereafter cooled to 0°C. To the mixture, ethyl acetate (20 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 60 ml. The combined aqueous layers were neutralized by the addition of 17 ml of concentrated acetic acid and thereafter extracted with ethyl acetate (4 x 60 ml). The organic layer was dried over magnesium sulphate and then removed to give a crude product with an optical purity of 59% ee. The residue, as an oil, (3.2 g) was dissolved in acetone (8 ml). A formed precipitate was filtered off. There was obtained 1.6 g of a crude produced of the desired compound as a white solid. The optical purity was shown to be 87% ee.

Example 15.

Asymmetric synthesis of (+)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ib).

5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.6 kg, 10.9 mol) was suspended in toluene (15 l). Water (8.9 ml, 0.49 mol), (+)-diethyl L-tartrate (460 g, 2.2 mol) and titanium(IV) isopropoxide (310 g, 1.09 mol) were added with stirring at 40°C. The mixture was stirred at 40°C for 50 minutes and then N,N-diisopropyl-ethylamine (190 ml, 1.09 mol) was added. The temperature was adjusted to 30°C and then cumene hydroperoxide (83%, 2.0 kg,

11 mol) was added and the oxidation was completed within 30 minutes. The crude mixture was shown to consist of 8.9% sulphide, 3.3% sulphone and 87% sulphoxide with an optical purity of 86% e.e. The product started to crystallize during the oxidation and was isolated from the reaction mixture by filtration. There was obtained 2.68 kg of the product with an optical purity of 96% e.e. The material was also shown to consist of 2.3% sulphide and 1.7% sulphone. The product was recrystallized in methanol/toluene. There was obtained 1.66 kg (yield: 44%) of the desired product with an optical purity of 99.7%. The content of sulphide and sulphone was less than 0.1% and 0.3% respectively.

Example 16.

Asymmetric synthesis of (-)-5-fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ib).

5-Fluoro-2-[[(4-cyclopropylmethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.6 kg, 10.9 mol) was suspended in toluene (14.4 l). Water (10 ml, 0.55 mol), (-)-diethyl D-tartrate (460 g, 2.2 mol) and titanium(IV) isopropoxide (310 g, 1.10 mol) were added with stirring at 40°C. The mixture was stirred at 40°C for 50 minutes and then N,N-diisopropyl-ethylamine (190 ml, 1.1 mol) was added. The temperature was adjusted to 35°C and then cumene hydroperoxide (83%, 2.0 kg, 11 mol) was added. The mixture was stirred for one hour at 35°C. The crude mixture was shown to consist of 8.7% sulphide, 4.8% sulphone and 85% sulphoxide with an optical purity of 78% e.e. The product started to crystallize during the oxidation and was isolated from the reaction mixture by filtration. There was obtained 2.78 kg of the product with an optical purity of 97% e.e. The material was also shown to consist of 1.9% sulphide and 2.5% sulphone. The product was recrystallized in methanol/toluene. There was obtained 1.67 kg (yield: 44%) of the desired product as off white crystals, 99.8% (e.e). The content of sulphide and sulphone was less than 0.1% and 0.6%, respectively.

Example 17.

Asymmetric synthesis of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ic).

3.4 g (9.1 mmol) of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole was suspended in toluene (20 ml). To the mixture was added 41 µl (2.3 mmol) of water, 1.7 ml (10 mmol) of (+)-diethyl L-tartrate and 1.3 g (4.6 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then 0.78 ml (4.5 mmol) of N,N-diisopropylethylamine was added. The mixture was cooled to 30°C and toluene (10 ml) was added. To the mixture was then added 1.7 ml (80%, 9.2 mmol) of cumene hydroperoxide. After a few minutes, more toluene (70 ml) was added and after one hour at 30°C, the mixture consisted of 12.5% sulphide, 3.5% sulphone and 84% sulphoxide with an optical purity of 95.6% e.e. The mixture was cooled to room temperature and a formed precipitate was filtered off. There was obtained 2.5 g of a crude product of the desired compound as a solid which was shown to have an optical purity of 98.2% e.e.

Example 18.

Asymmetric synthesis of (-)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ic)

Titanium (IV) isopropoxide (7.5 ml, 25 mmol) and water (0.45 ml, 25 mmol) were added with stirring to a mixture of (-)-diethyl D-tartrate (8.6 ml, 50 mmol) and methylene chloride (50 ml). The solution was stirred for 30 minutes at room temperature and then 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1-H-benzimidazole (9.3 g, 25 mmol) and diisopropylethylamine (1.25 ml, 7.2 mmol) were introduced. At room temperature cumene hydroperoxide (tech, 80%, 5.1 ml, 27 mmol) was added and reacted for 3 h at room temperature. The crude product consisted of a crude sulphoxide with an enantiomeric excess (e.e.) of 71% . After purification on silica gel with

methanol/methylene chloride as eluent followed by repeated crystallisations from ethanol there was obtained 2.9 g (30%) of the title compound with an enantiomeric excess of 99.4%.

Example 19.

Asymmetric synthesis of (-)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ic).

4.7 g (12.5 mmol) of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole was dissolved in methylene chloride (100 ml). To the solution was added 80 µl (4.5 mmol) of water, 3.2 ml (19 mmol) of (-)-diethyl D-tartrate and 2.2 ml (7.5 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at reflux and then cooled to room temperature. 0.88 ml (5.0 mmol) of N,N-diisopropylethylamine was added and the mixture was then stirred for 30 minutes. 2.15 ml (12 mmol) cumene hydroperoxide (80%) was added and after 2 h at room temperature the mixture consisted of 23% sulphide and 72% sulphoxide with an optical purity of 88% e.e. To the mixture, methylene chloride (100 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 300 ml. The combined aqueous layers were neutralized by the addition of 50 ml of concentrated acetic acid, after which white crystals started to precipitate. The crystals was filtered off, washed with diethyl ether and dried to give 2.34 g (48%) white crystals of the title compound consisted of 1.5% sulphide and 1.8% sulphone with an optical purity of 92% e.e.

Example 20.

Asymmetric synthesis of (+)-5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ic).

4.7 g (12.5 mmol) of 5-carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole was dissolved in methylene chloride (100 ml). To the solution was added 80 µl (4.5 mmol) of water, 3.2 ml (19 mmol) of (+)-diethyl L-tartrate and 2.2 ml (7.5 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at reflux and then cooled to room temperature. 1.1 ml (6.3 mmol) of N,N-diisopropylethylamine was added and the mixture was then stirred for 30 minutes. 2.15 ml (12 mmol) cumene hydroperoxide (80%) was added and after 2 h at room temperature the mixture consisted of 19% sulphide and 77% sulphoxide with an optical purity of 90% e.e. To the mixture, methylene chloride (100 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 300 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (50 ml) which afforded white crystals. The crystals were filtered off, washed with diethyl ether and dried to give 3.29 g (68%) of white crystals of the title compound with an optical purity of 93% e.e. The material also consisted of 2.2% sulphide and 0.9% sulphone.

Example 21.

Asymmetric synthesis of (-)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (-)-(Id).

2.1 g (6.0 mmol) of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole was dissolved in toluene (50 ml). To the solution was added 65 µl (3.6 mmol) of water, 2.6 ml (15.0 mmol) of (-)-diethyl D-tartrate and 1.8 ml (6.0 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled to room temperature. 1.05 ml (6.0 mmol) of N,N-diisopropylethylamine and 1.1 ml (6.0 mmol) of cumene hydroperoxide

(80%) were added. After stirring for 16 h at room temperature the mixture consisted of 11% sulphide, 7% sulphone and 78% sulphoxide according to achiral HPLC. To the mixture 50 ml toluene was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 150 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (30 ml). Thereafter, the workup procedure employed extraction, evaporation and flash chromatography yielding 1.2 g of the title compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess (e.e.) of 55% (chiral analysis). After treating the residue with acetonitrile there was obtained a precipitate that was removed by filtration. Evaporation of the filtrate afforded an oil with enhanced optical purity. Repeating this procedure a couple of times afforded 0.63 g (29%) of the desired compound as an oil with an optical purity of 99.5% e.e.

Example 22.

Asymmetric synthesis of (+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (+)-(Id).

2.1 g (6.0 mmol) of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole was dissolved in 50 ml of toluene. To the solution was added 65 µl (3.6 mmol) of water, 2.6 ml (15.0 mmol) of (+)-diethyl L-tartrate and 1.8 ml (6.0 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled to room temperature. 1.05 ml (6.0 mmol) of N,N-diisopropylethylamine and 1.1 ml (6.0 mmol) of cumene hydroperoxide (80%) were added. After stirring for 16 h at room temperature the mixture consisted of 13% sulphide, 8% sulphone and 76% sulphoxide according to achiral HPLC. To the mixture toluene (50 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 150 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (30 ml). Thereafter, the workup procedure employed extraction, evaporation and flash chromatography yielding 0.85 g of the title

compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess (e.e.) of 46% (chiral analysis). After treating the residue with acetonitrile there was obtained a precipitate that was removed by filtration. Evaporation of the filtrate afforded an oil with enhanced optical purity. Repeating this procedure a couple of times afforded 0.31 g (14%) of the desired compound as an oil with an optical purity of 99.6% e.e.

Example 23.

Asymmetric synthesis of (-)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (-)-(Ie).

1.1 g (3.0 mmol) of 5-difluoromethoxy -2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole was dissolved in methylene chloride (25 ml). To the solution were added 20 µl (1.1 mmol) of water, 0.81 ml (4.7 mmol) of
(-)-diethyl D-tartrate and 0.56 ml (1.9 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at reflux and then cooled to room temperature. Thereafter, 0.22 ml (1.3 mmol) of N,N-diisopropylethylamine was added followed by the addition of 0.57 ml (80%, 3.1 mmol) cumene hydroperoxide (80%). After 21 h at room temperature the mixture consisted of 10% sulphide and 89% sulphoxide with an optical purity of 86% e.e. To the mixture, methylene chloride (25 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 300 ml. The combined aqueous layers were neutralized by the addition of 25 ml of concentrated acetic acid and thereafter extracted with methylene chloride (3 x 100 ml). The residue, as an oil, (1.16 g) was dissolved in hot acetonitrile (20 ml). A white precipitate was formed when the solution was cooled to room temperature and there was obtained 0.35 g (29%) of the desired compound by filtration. There was also obtained 0.71 g of the desired compound with a lower optical purity from the filtrate by evaporation thereof. The optical purity of the crystals and the filtrate was shown to be 97.4% e.e. and 75% ee. respectively.

Example 24.

Asymmetric synthesis of (+)-5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1H-benzimidazole, (+)-(Ie).

1.1 g (3.0 mmol) of 5-difluoromethoxy -2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole was dissolved in methylene chloride (25 ml). To the solution were added 20 µl (1.1 mmol) of water, 0.81 ml (4.7 mmol) of (+)-diethyl L-tartrate and 0.56 ml (1.9 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at reflux and then cooled to room temperature. Thereafter, 0.22 ml (1.3 mmol) of N,N-diisopropylethylamine was added followed by the addition of 0.57 ml (80%, 3.1 mmol) cumene hydroperoxide (80%). After 21 h at room temperature the mixture consisted of 8% sulphide and 92% sulphoxide with an optical purity of 87% e.e. To the mixture, methylene chloride (25 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 300 ml. The combined aqueous layers were neutralized by the addition of 25 ml of concentrated acetic acid and thereafter extracted with methylene chloride (3 x 100 ml). The solvent was removed and the residue, as an oil, (0.86 g) was dissolved in hot acetonitrile (20 ml). A white precipitate was formed when the solution was cooled to room temperature and there was obtained 0.36 g (30%) of the desired compound by filtration. There was also obtained 0.48 g of the desired compound with a lower optical purity from the filtrate by evaporation thereof. The optical purity of the crystals and the filtrate was shown to be 97.4% e.e. and 78% ee. respectively.

Example 25.

Asymmetric synthesis of (-)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (-)-(If).

2.1 g (6.3 mmol) of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazole was dissolved in 50 ml of toluene. To the solution was added 40 µl (2.2 mmol) of water, 1.6 ml (9.4 mmol) of (-)-diethyl D-tartrate and 1.1 ml (3.8 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled to room temperature. 0.44 ml (2.6 mmol) of N,N-diisopropylethylamine and 1.1 ml (6.0 mmol) of cumene hydroperoxide (80%) were added. After stirring for 2 h at room temperature the mixture consisted of 9% sulphide, 4% sulphone and 86% sulphoxide according to achiral HPLC. To the mixture toluene (50 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 150 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (30 ml). Thereafter, the workup procedure employed extraction, evaporation and flash chromatography yielding 1.62 g of the title compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess (e.e.) of 90% (chiral analysis). After treating the material with acetonitrile there was a precipitate that could be removed by filtration. Concentrating the filtrate afforded 1.36 g (60%) of the title compound as an oil with an optical purity of 91.5% e.e.

Example 26.

Asymmetric synthesis of (+)-2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulphinyl]-1H-benzimidazole, (+)-(If).

2.1 g (6.3 mmol) of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazole was dissolved in 50 ml of toluene. To the solution was added 40 µl (2.2 mmol) of water, 1.6 ml (9.4 mmol) of (+)-diethyl L-tartrate and 1.1 ml (3.8 mmol) of titanium(IV) isopropoxide. The mixture was stirred for 60 minutes at 50°C and then cooled to room temperature. 0.44 ml (2.6 mmol) of N,N-

diisopropylethylamine and 1.1 ml (6.0 mmol) of cumene hydroperoxide (80%) were added to the solution. After stirring for 2 h at room temperature the mixture consisted of 9% sulphide, 4% sulphone and 85% sulphoxide according to HPLC. To the mixture toluene (50 ml) was added and the resultant solution was extracted three times with an aqueous ammonia (12%) solution with a total volume of 150 ml. The combined aqueous layers were neutralized by the addition of concentrated acetic acid (30 ml). Thereafter, the workup procedure employed extraction, evaporation and flash chromatography yielding 1.63 g of the title compound with a purity of 99.9% (achiral analysis) and with an enantiomeric excess (e.e.) of 91% (chiral analysis). After treating the material with acetonitrile, there was a precipitate that could be removed by filtration. Concentrating the filtrate afforded 1.1 g (49%) of the title compound as an oil with an optical purity of 96.0% e.e.

Example 27.

Asymmetric synthesis of (-)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]benzimidazole, (-)-(Ig).

2.0 g (6.1 mmol) of 2-[2-(N-isobutyl-N-methylamino)benzylthio]-benzimidazole was dissolved in toluene (6 ml). While stirring, 40 µl (2.2 mol) of water, 1.6 ml (9.3 mmol) of (+)-diethyl L-tartrate and 1.1 ml (3.7 mmol) of titanium (IV) isopropoxide were added at 50 °C. The resulting mixture was stirred at 50 °C for 1 hour and then 0.53 ml (3.0 mmol) of N,N-diisopropylethylamine was added. The reaction mixture was then cooled to 30 °C whereupon 1.1 ml (6.1 mmol) of cumene hydroperoxide (80%) was added. The mixture was stirred at 30 °C for 50 min.Analysis of the reaction mixture indicated that the optical purity of the formed sulphoxide was 92% e.e. The mixture was cooled to room temperature and diluted with small amount of methylene chloride. Column chromatography [silica gel, eluted with 4% MeOH/CH_2Cl_2(NH_3 saturated)] yielded an oil which was re-chromatographed (silica gel, eluted with 20% EtOAc/hexane). The obtained (1.6 g) crude product, as an oil was treated with a small amount of

acetonitrile in order to enhance the optical purity. A formed precipitate (270 mg) was removed by filtration. The solvent of the filtrate was removed yielding 1.2 g of the desired compound as an oil. The optical purity of the material was 96% e.e.

Example 28.

Asymmetric synthesis of (+)-2-[2-(N-isobutyl-N-methylamino)benzylsulphinyl]benzimidazole, (+)-(Ig).

2.0 g (6.1 mmol) of 2-[2-(N-isobutyl-N-methylamino)benzylthio]-benzimidazole was dissolved in toluene (6 ml). While stirring, 40 µl (2.2 mmol) of water, 1.6 ml (9.3 mmol) of (-)-diethyl D-tartrate and 1.1 ml (3.7 mmol) of titanium (IV) isopropoxide were added at 50 °C. The resulting mixture was stirred at 50 °C for 1 hour and then 0.53 ml (3.0 mmol) of N,N-diisopropylethylamine was added. The reaction mixture was then cooled to 30 °C whereupon 1.1 ml (6.1 mmol) of cumene hydroperoxide (80%) was added. The mixture was stirred at 30 °C for 50 min. Analysis of the reaction mixture indicated that the optical purity of the formed sulphoxide was 91% e.e. The mixture was cooled to room temperature and diluted with small amount of methylene chloride. Column chromatography [silica gel, eluted with 4% MeOH/CH_2Cl_2(NH_3 saturated)] yielded crude product as an oil. This material was treated with a mixture of ethyl acetate and hexane (10% EtOAc). A formed precipitate (140 mg) was removed by filtration. The solvent of the filtrate was removed yielding 0.95 g of the desired compound as an oil. The optical purity of the material was 96% e.e

Example 29

Asymmetric synthesis of two of the stereoisomers of 2-[(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[*b*]pyridin-9-yl)sulphinyl]-1H-benzimidazole, (Ih).

In the following example, the first diastereomer of the title compound eluted on straight phase (silica gel) is named diastereomer A and second as diastereomer B.

Synthesis: 0.51 g (1.57 mmol) of the racemate of 2-[(4-methoxy-6,7,8,9- tetrahydro-5H-cyclohepta[*b*]-pyridin-9-yl)thio]-1H-benzimidazole was suspended in 20 ml of toluene. Under stirring at room temperature, 0.34 g (1.6 mmol) of (+)-diethyl L-tartrate, 7µl (0.4 mmol) of water and 0.22 g (0.78 mmol) of titanium(IV) isopropoxide were added. The mixture was stirred at 50°C for 50 minutes and then 100 mg (0.78 mmol) of N,N-diisopropylethylamine was added at room temperature. The addition of 0.33 g (160 mmol) cumene hydroperoxide (80%) was then performed over a period of 5 minutes at room temperature whereupon the solution was stirred at room temperature for 24 hours.The stereoisomeric composition of the title compound in the crude mixture was as follows; The ratio of diastereomers was 4:3 in favour of diastereomer A. The optical purity of the (-)-enantiomer of diastereomer A was 76% e.e. and the optical purity of the (+)-enantiomer of diastereomer B was 68% e.e. The product mixture was washed with water (3x25 ml) dried over Na_2SO_4 and the solvent removed. Flash chromatography of the residue (methanol-methylene chloride 0 to 5%) yielded 0.25 g (47%) of the enantiomeric enriched diastereomeric sulphoxide as a syrup.

Separation of the diastereomers. A repeated chromatographic preparation (methanol-methylene chloride 0 to 5%) afforded a separation of the two diastereomers. Thus, the (-)-enantiomer of diastereomer A was obtained as a syrup (0.14 g) with an optical purity of 77% e.e. The (+)-enantiomer of diastereomer B was also obtained as a syrup (0.085 g) with an optical purity of

68% e.e. , however, diastereomer B was contaminated with ca. 10% of diastereomer A.

Optical purification: The optical purity of the (-)-enantiomer of diastereomer A was enhanced by the addition of ca. 2 ml of acetonitrile to the enantiomerically enriched preparation of diastereomer A (0.14 g). After stirring over night, the formed precipitate (almost racemic diastereomer A) was filtered off and the solvent of the filtrate was removed by film evaporation. Thus, there was obtained 85 mg of the (-)-enantiomer of diastereomer A as a syrup with an optical purity of 88% e.e. The optical purity of the (+)-enantiomer of the diastereomer B was enhanced in a similar way. Thus, by addition of acetonitrile (2 ml) to the enantiomerically enriched preparation of diastereomer B (0.085 g) followed by stirring over night resulted in a precipitate which was filtered off. There was obtained 0.050 g of the (+)-enantiomer of diastereomer B with an optical purity of 95% e.e.

The best mode to carry out the present invention known at present is as described in Example 11.

Reference Example A.

Oxidation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole using tert-butyl hydroperoxide under neutral conditions. (The method used is in accordance with the method used in Euro. J. Biochem. 166 (1987) 453-459 and described in J. Am. Chem. Soc. 106 (1984) 8188).

Water (90µl, 5 mmol) was added at room temperature to a solution of (+)-diethyl L-tartrate (1.7 ml, 10 mmol) and titanium (IV) isopropoxide (1.5 ml, 5 mmol) in 50 ml methylene chloride. After 20 minutes 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (6.6 g, 5 mmol) was dissolved in the reaction mixture and the solution was cooled to -20°C. A 3 M solution of tert-butyl hydroperoxide in toluene (1.8 ml, 5.5 mmol) was added and the mixture was kept

at -20°C for 120 h. After this time the mixture consisted of 28% of sulphide (starting material), 8.6% sulphone, 30.6% (-)-enantiomer of sulphoxide and 28.1% (+)-enantiomer of sulphoxide (i.e. ee=4%) . In a similar experiment run at +8°C for 7 h the mixture consisted of 32.4% of sulphide, 8.7% sulphone, 24.6% (-)-enantiomer of sulphoxide and 26.7% (+)-enantiomer of sulphoxide (i.e. ee=4%).

Reference Example B.

Oxidation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole using cumene hydroperoxide at -22°C without addition of a base. (The oxidation method used is described in Tetrahedron (1987), 43, 5135.)

The experiment was performed using the same conditions as in Reference A with the exception that cumene hydroperoxide was used instead of tert-butyl hydroperoxide. After 120 at -22°C the mixture consisted of 29% sulphide, 3.8% sulphone, 29.1% (-)-enantiomer of sulphoxide and 35.5% (+)-enantiomer of sulphoxide (i.e. ee=10%).

Reference Example C.

Oxidation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole using cumene hydroperoxide under neutral conditions.

Water (450 µl, 25 mmol) was added at room temperature to a solution of (+)-diethyl L-tartrate (8.5 ml, 50 mmol) and titanium (IV) isopropoxide (7.4 ml, 25 mmol) in 50 ml methylene chloride. After 20 minutes 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (8.2 g, 25 mmol) was added and the mixture was divided in 3 portions. To one of the portions cumene hydroperoxide (1.7 ml 80% soln, 9.2 mmol) was added at room temperature, and a sample was removed after 3 h and 20 minutes. The mixture consisted of 29.4% sulphide, 6.3% sulphone, 22.0% (-)-enantiomer of sulphoxide and 35% (+)-enantiomer of sulphoxide (ii.e. ee=23%).

Reference Example D.

Oxidation of 5-methoxy-2-[[(4-methoxy-3.5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole using cumene hydroperoxide with the addition of a base, according to one aspect of the present invention.

The experiment was performed using the same conditions as in Reference Example C with the additional feature that one equivalent of diisopropylethylamine was added together with the cumene hydroperoxide. After 3 h and 20 minutes the mixture consisted of 17.2% sulphide, 3.5% sulphone, 8.7% (-)-enantiomer of sulphoxide and 69.3% (+)-enantiomer of sulphoxide (i.e. ee=78%).

Reference Example E.

Asymmetric synthesis of (+)-2-[5-(3,5-dimethylpyrazol-1-yl)pentylsulphinyl]-4,5-diphenylimidazole.

0.8 g (1.9 mmol) of 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole was dissolved in toluene (20 ml). The solution was concentrated on a rotavapor until half the volume was removed. To the mixture was added 20 µl (1.1 mmol) of water, 1.0 g (4.8 mmol) of (+)-diethyl L-tartrate and 0.54 g (1.9 mmol) of titanium(IV) isopropoxide in the given order. The mixture was stirred for 60 minutes at 50°C and then 0.25 g (1.9 mmol) of N,N-diisopropylethylamine was added. The mixture was then stirred at room temperature for 30 minutes whereupon 0.36 g (80%, 1.9 mmol) of cumene hydroperoxide was added. The mixture was stirred for four hours at room temperature and then the reaction was shown to be completed. The solution was washed with water (2 ml) and then the organic layer was removed. The oily residue was purified by chromatography on silica gel (methanol-methylene chloride 0 to 5%). There was obtained 0.7 g of the desired product as an oil which was shown to have an optical purity of 87% e.e.

Reference Example F.

Asymmetric synthesis of (-)-2-[5-(3,5-dimethylpyrazol-1-yl)pentylsulphinyl]-4,5-diphenylimidazole.

1.5 g (3.6 mmol) of 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole was dissolved in toluene (40 ml). The solution was concentrated on a rotavapor until half the volume was removed. To the mixture was added 38 µl (2.1 mmol) of water, 1.85 g (9.0 mmol) of (-)-diethyl D-tartrate and 1.01 g (3.6 mmol) of titanium(IV) isopropoxide in the given order. The mixture was stirred for 60 minutes at 50°C. The mixture was divided in two parts and then 0.23 g (1.9 mmol) of N,N-diisopropylethylamine was added to half the mixture. This mixture was then stirred at room temperature for 15 minutes whereupon 0.35 g (80%, 1.8 mmol) of cumene hydroperoxide was added. The mixture was stirred for four hours at room temperature and then the reaction was shown to be completed. The solution was stirred with water (2 ml) and then the organic layer was removed. The oily residue was purified by chromatography on silica gel (methanol-methylene chloride 0 to 5%). There was obtained 0.65 g of the desired product as an oil which was shown to have an optical purity of 92% e.e.

Conclusion:

The examples show that the highest enantiomeric excess is obtained if all aspects of the invention are taken into consideration. The addition of a base during the oxidation is essential for a high enantioselectivity according to one aspect of the invention. But a high enantiomeric excess may also be obtained according to other aspects of the invention if the order of addition of components into the reaction vessel is altered, and alternatively the time and/or temperature during the preparation of the chiral titanium complex is taken into consideration. The preparation of the chiral titanium complex is preferably performed in the presence of the prochiral sulphide and during an elevated temperature and a prolonged time.

Determination of enantiomeric excess in the Examples and Reference Examples.

The enantiomeric excess value in each example given above gives an indication of the relative amounts of each enantiomer obtained. The value is defined as the difference between the relative percentages for the two enantiomers. Thus, for example, when the percentage of the (-)-enantiomer of the formed sulphoxide is 97.5% and the percentage for the (+)-enantiomer is 2.5%, the enantiomeric excess for the (-)-enantiomer is 95%.

The enantiomeric composition of the obtained sulphoxide has been determined by chiral High Performance Liquid Chromatography(HPLC) on either a Chiralpak AD Column® or a Chiral AGP Column® under the following conditions, specified for each compound:

Compound of formula (Ia).

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (100 ml), ethanol (100 ml) and acetic acid (10µl)
Flow	0.5 ml/min
Inj.vol.	50 µl
Wavelength	302 nm

Retention time for the (-)-enantiomer 4.0 min

Retention time for the (+)-enantiomer 5.8 min

Compound of formula (Ib).

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (125 ml), 2-propanol (25 ml), ethanol (50 ml) and acetic acid (30µl)
Flow	0.4 ml/min
Inj.vol.	50 µl
Wavelength	287 nm

Retention time for the (+)-enantiomer 6.5 min

Retention time for the (+)-enantiomer 13.8 min

Compound of formula (Ic).

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (100 ml), ethanol (100 ml) and acetic acid (10µl)
Flow	0.4 ml/min
Inj.vol.	50 µl
Wavelength	300 nm

Retention time for the (+)-enantiomer 6.4 min

Retention time for the (-)-enantiomer 9.4 min

Compound of formula (Id).

Column	Chiral-AGP 100x4.0 mm
Eluent	Sodium phosfate buffer solution (pH 7.0) I=0.025 (500 ml) and acetonitrile (70 ml)
Flow	0.5 ml/min
Inj.vol.	20 µl
Wavelength	210 nm

Retention time for the (+)-enantiomer 6.2 min

Retention time for the (-)-enantiomer 7.2 min

Compound of formula (Ie).

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (150 ml), ethanol (50 ml) and acetic acid (10µl)
Flow	0.5 ml/min
Inj.vol.	50 µl
Wavelength	290 nm

Retention time for the (-)-enantiomer 9.5 min

Retention time for the (+)-enantiomer 13.3 min

Compound of formula (If).

Column	Chiral-AGP 100x4.0 mm
Eluent	Sodium phosfate buffer solution (pH 7.0) I=0.025 (430 ml) and acetonitrile (70 ml)
Flow	0.5 ml/min
Inj.vol.	20 µl
Wavelength	210 nm

Retention time for the (+)-enantiomer 4.1 min

Retention time for the (-)-enantiomer 6.8 min

Compound of formula (Ig).

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (200 ml) and ethanol (10 ml)
Flow	0.5 ml/min
Inj.vol.	50 µl
Wavelength	285 nm

Retention time for the (-)-enantiomer 9.0 min

Retention time for the (+)-enantiomer 9.8 min

Compound of formula (Ih).

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (150 ml) and 2-propanol (50 ml)
Flow	0.4 ml/min
Inj.vol.	50 µl
Wavelength	285 nm

Retention time for the (-)-enantiomer of diasteremor A 6.9 min
Retention time for the (+)-enantiomer of diasteremor A 8.1 min
Retention time for the (+)-enantiomer of diasteremor B 8.8 min
Retention time for the (-)-enantiomer of diasteremor B 11.0 min

The first diastereomer of compound (Ih) eluted on straight phase (achiral silica gel, see below) is named diastereomer A and second as diastereomer B.

Reference Examples E and F.

In Reference Examples E and F, the enantiomeric composition of the products was determined by chiral HPLC using following conditions:

Column	Chiralpak AD 50x4.6 mm
Eluent	iso-Hexane (200 ml), ethanol (5 ml) and acetic acid (10µl)
Flow	1 ml/min
Inj.vol	50 µl
Wave lenght	280 nm

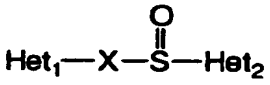
Retention time for the (+)-enantiomer 13.5 min
Retention time for the (-)-enantiomer 17.3 min

It is to be noted that in the Examples referring to the single enantiomers of omeprazole or its alkaline salts, the sign of the optical rotation of single

enantiomeric form of omeprazole sodium salt measured in water is the opposite of that of the sign when measured said compound in its neutral form in chloroform.

Claims

1. A process for enantioselective synthesis of a sulphoxide compound of formula (I) or an alkaline salt thereof either as a single enantiomer or in an enantiomerically enriched form



I

wherein

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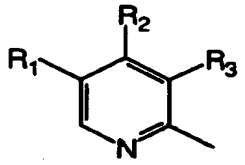

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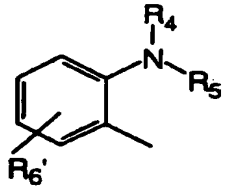

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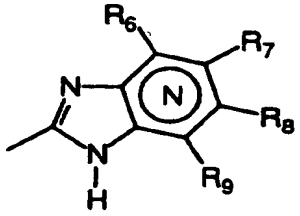
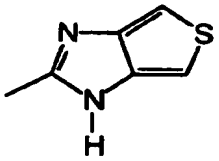
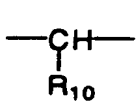


or



and X is



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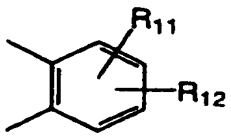

wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optinally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

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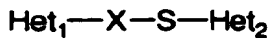
R_{10} is hydrogen or forms an alkylene chain together with R_3;

R_{11} and R_{12} are the same of different and selected from hydrogen, halogen or alkyl

and alkyl groups, alkoxy groups and moities thereof may be branched or straight C_1-C_9-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl

characterized in that a pro-chiral sulphide of the formula II

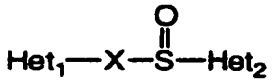


II

wherein Het_1 and Het_2 are as defined above,

is oxidised in an organic solvent with an oxidising agent and in the presence of a chiral titanium complex and a base, and the obtained sulphoxide optionally is converted into a pharmaceutically acceptable salt by conventional processes.

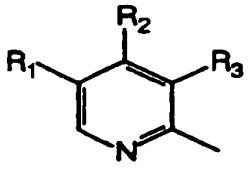
2. A process for enantioselective synthesis of a sulphoxide of formula I either as a single enantiomer or in an enantiomerically enriched form



I

wherein

Het_1 is



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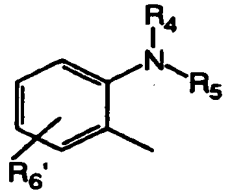
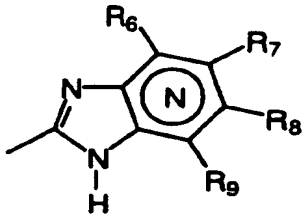


Het_2 is



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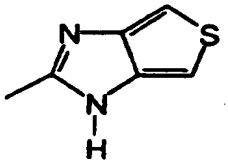
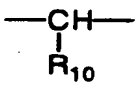


and X is



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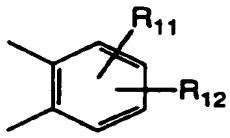

wherein

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R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optinally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

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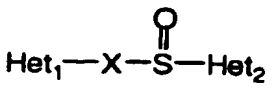
characterized in that a pro-chiral sulphide of the formula II

$$Het_1—X—S—Het_2 \qquad II$$

wherein Het_1 and Het_2 are as defined above,

is oxidised in an organic solvent with an oxidising agent and in the presence of a chiral titanium complex, optionally in the presence of a base, wherein the titanium complex has been prepared in the presence of the pro-chiral sulphide, and the obtained sulphoxide optionally is converted into a pharmaceutically acceptable salt by conventional processes.

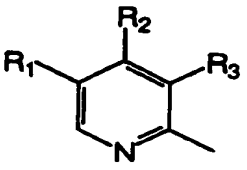
3. A process for enantioselective synthesis of a sulphoxide of formula either as a single enantiomer or in an enantiomerically enriched form



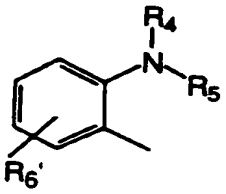
1

wherein

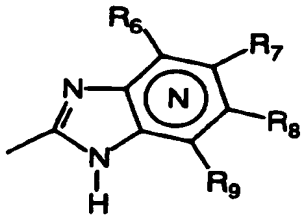
Het_1 is



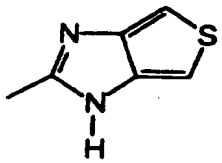
or



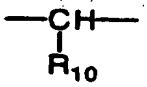
Het_2 is



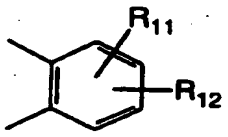
or



and X is



or



wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

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R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

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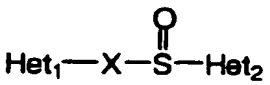
characterized in that a pro-chiral sulphide of the formula II

$$Het_1—X—S—Het_2 \qquad II$$

wherein Het_1 and Het_2 are as defined above,

is oxidised in an organic solvent with an oxidising agent and in the presence of a chiral titanium complex, optionally in the presence of a base, wherein the titanium complex has been prepared during an elevated temperature and/or a prolonged preparation time, and the obtained sulphoxide optionally is converted into a pharmaceutically acceptable salt by conventional processes.

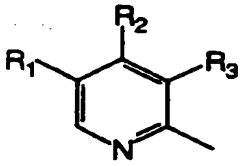
4. A process for enantioselective synthesis of a sulphoxide of formula I either as a single enantiomer or in an enantiomerically enriched form



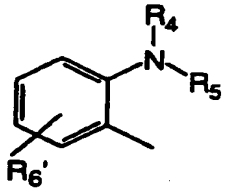
I

wherein

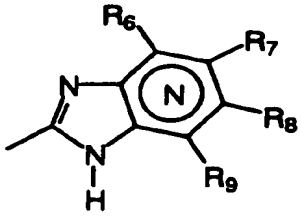
Het_1 is



or



Het_2 is



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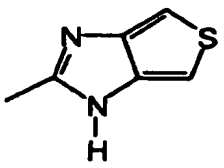
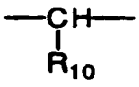


and X is



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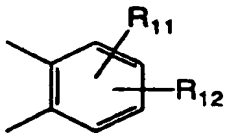

wherein

N inside the benzene ring of the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkylthio, alkoxy optinally substituted by fluorine, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenylalkyl and phenylalkoxy;

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R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

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R_{10} is hydrogen or forms an alkylene chain together with R_3;

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and alkyl groups, alkoxy groups and moities thereof may be branched or straight C_1-C_9-chains or comprise cyclic alkyl groups, for example cycloalkylalkyl

5

characterized in that a pro-chiral sulphide of the formula II

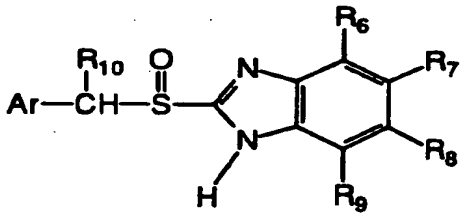
$$Het_1—X—S—Het_2 \qquad II$$

wherein Het_1 and Het_2 are as defined above,

10

is oxidised in an organic solvent with an oxidising agent and in the presence of a chiral titanium complex, optionally in the presence of a base, wherein the titanium complex is prepared in the presence of the pro-chiral sulphide and during an elevated temperature and/or during a prolonged preparation time, and the
15 obtained sulphoxide optionally is converted into a pharmaceutically acceptable salt by conventional processes.

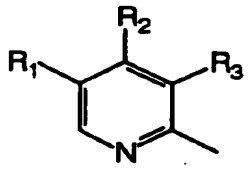
5. A process according to any of claims 1 - 4, wherein the sulphoxides prepared by the process are sulphoxides defined by formula I' either as a single enantiomer
20 or in an enantiomerically enriched form:



(I')

wherein

Ar is



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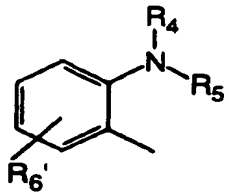
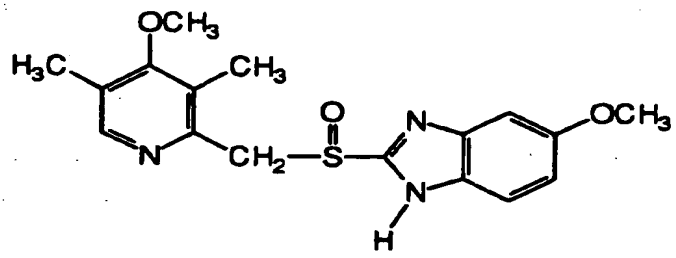
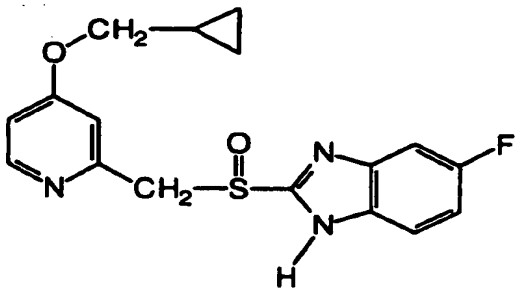


and R_1 - R_{10} are the same as defined in any of claims 1 - 4.

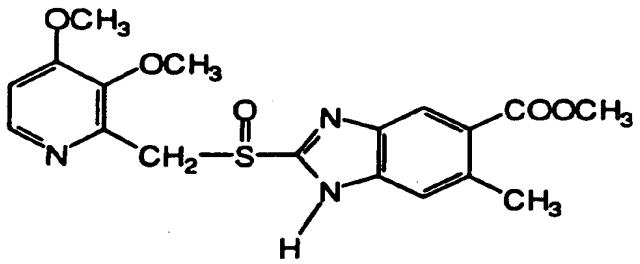
6. A process according to any of claims 1 - 4, wherein the sulphoxides prepared by the process are sulphoxides according to any of the formula (Ia) to (Ih) either as a single enantiomer or in an enantiomerically enriched form:



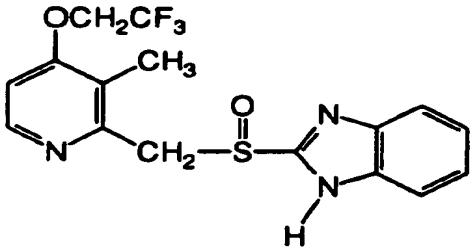
(Ia)



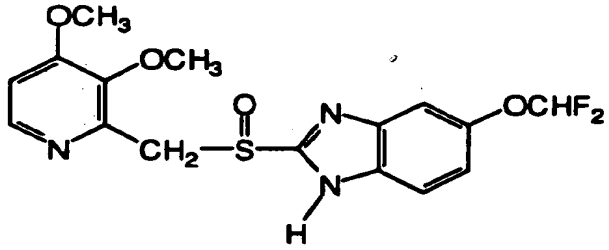
(Ib)



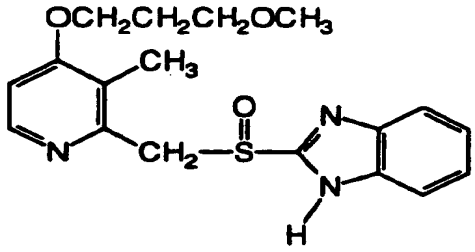
(Ic)



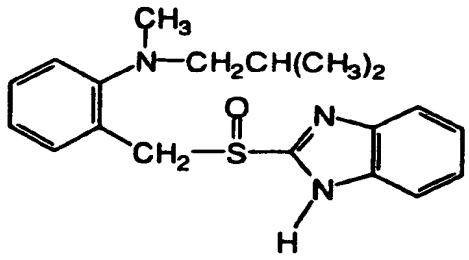
(Id)



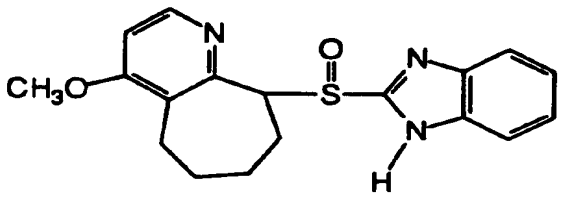
(Ie)



(If)



(Ig)



(Ih)

7. A process according to any of claims 1 - 4, characterized in that the pro-chiral sulphide of formula II is oxidised with an oxidising agent in the form of cumene hydroperoxide.

8. A process according to any of claims 1 - 4, characterized in that the titanium complex is prepared from a titanium(IV) compound.

9. A process according to claim 8, characterized in that the titanium(IV) compound is a titanium(IV) alkoxide.

10. A process according to claim 9, characterized in that the titanium(IV) alkoxide is titanium(IV) isopropoxide.

11. A process according to any of claims 1 - 4, characterized in that the chiral ligand in the titanium complex is a chiral branched or unbranched alkyl diol or an aromatic diol.

12. A process according to claim 11, characterized in that the chiral diol is a chiral ester of tartaric acid.

13. A process according to claim 12, characterized in that the chiral ester is selected from the group of (+)-diethyl L-tartrate and (-)-diethyl D-tartrate.

14. A process according to any of claims 1 - 4, characterized in that the amount of chiral titanium complex is 0.05 - 0.50 equivalents.

15. A process according to any of claims 1 - 4, characterized in that the oxidation reaction is carried out at a temperature between 20 - 40 °C , preferably at room temperature.

16. A process according to any of claims 1 - 4, characterized in that the organic solvent is selected from the group of toluene and ethyl acetate.

17. A process according to any of claims 1 - 4, characterized in that the oxidation is carried out in the presence of a base selected from the group of organic bases.

18. A process according to claim 17, characterized in that the base is an amine.

19. A process according to claim 18, characterized in that the amine is selected from the group of triethylamine and N,N-diisopropylethylamine.

20. A process according to any of claims 3 - 4, characterized in that a prolonged preparation time for preparation of the chiral titanium complex is 1 - 5 hours.

21. A process according to any of claims 3 - 4, characterized in that an elevated temperature for preparation of the chiral complex is 30-70°C.

22. A process according to any of claims 1 - 4, characterized in that the process further comprise a step for treating the product formed with an aqueous ammonia solution.

23. A process according to any of claims 1 - 4, characterized in that the process further comprises steps for crystallisation of the obtained crude product.

24. (+)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof produced in accordance with any of the claims 1 - 23.

25. (-)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof in accordance with any of the claims 1 - 23.

26. (+)-5-Fluoro-2-(((4-cyclopropylmethoxy-2-pyridinyl)methyl)sulphinyl)-1H-benzimidazole or a pharmaceutically acceptable salt thereof produced in accordance with any of the claims 1 - 23.

27. (-)-5-Fluoro-2-(((4-cyclopropylmethoxy-2-pyridinyl)methyl)sulphinyl)-1H-benzimidazole or a pharmaceutically acceptable salt thereof produced in accordance with any of the claims 1 - 23.

28. (-)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof produced in accordance with any of the claims 1 -23.

29. (+)-5-Carbomethoxy-6-methyl-2-[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof produced in accordance with any of the claims 1 -23.

30. One of the single enantiomers of 2-[5-(3,5-dimethylpyrazol-1-yl)pentyl-sulphinyl]-4,5-diphenyl imidazole prepared by a process described in any of the claims 1 - 4.

31. One of the single enantiomers of 2(((4-(3-methoxypropoxy)-3-methyl-2-pyridinyl)methyl)sulphinyl)-1H-benzimidazole or a pharmaceutically acceptable salt thereof.

32. One of the single enantiomers of 2(2-(N-isobutyl-N-methylamino)benzyl-imidazole or a pharmaceutically acceptable salt thereof.

33. One of the four stereoisomers of 2((4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta(*b*)pyridin-9-yl)sulphinyl)-1H-benzimidazole or a pharmaceutically acceptable salt thereof.

34. Use of the compounds defined in any of claims 24 - 33 in medicine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00818

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, C07D 235/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Eur. J. Biochem, Volume 166, 1987, Kristine Sigrist-Nelson et al, "Ro 18-5364, a potent new inhibitor of the gastric (H + K)-ATPase" page 453 - page 459 --	1-23
A	J. Am. Chem. Soc., Volume 106, 1984, P. Pitchen et al, "An Efficient Asymmetric Oxidation of Sulfides to Sulfoxides" page 8188 - page 8193 --	1-23
X	DE 4035455 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 14 May 1992 (14.05.92) --	24,25,34

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 1995	07 -11- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00818

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. Pharm. Bull., Volume 42, No 3, March 1994, Shin-ichi Yamada et al, "Syntheses and Antiulcer Activities of Novel 2-((6,7,8, 9-Tetrahydro-5H-Cyclohepta(b)Pyridin-9-Yl)Sulfinyl) -1H-Benzimidazole Analogues" page 718 - page 720 -- --------	33,34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00818

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-15,19-21
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [X] Claims Nos.: 30 and 32
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The compounds according to claims 30 and 32 are not included in formula I in claim 1. According to Article 6, the claims shall be clear and concise.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/10/95

International application No.
PCT/SE 95/00818

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A1- 4035455	14/05/92	AU-A- 8840691	11/06/92
		WO-A- 9208716	29/05/92